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SYMPATHETIC ACTIVITY IN CERTAIN DISEASES, ESPECIALLY THOSE OF THE PERIPHERAL CIRCULATION *

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Fundamental facts concerning the anatomy and the physiology of the sympathetic nervous system lay dormant for many decades. At the end of the nineteenth century, several attempts were made to influence the course of epilepsy, exophthalmic goiter and glaucoma by interrupting or excising parts of the cervical sympathetic chain. These efforts had been almost forgotten, owing to the poor results achieved, when, in 1916, Jonnesco attracted the attention of the medical world by performing cervical sympathectomy for angina pectoris. The interest in the removal of the sympathetic influence was greatly quickened by Leriche's work on periarterial sympathectomy, which he first employed in 1917 in the treatment for causalgia and in subsequent years for other conditions attributed to vasomotor disturbances. The eradication of visceral pain by interrupting sympathetic impulses, either temporarily as a diagnostic measure or permanently at operation, further attracted attention in recent years to this system. This interest, however, has been greatly stimulated since the work of Hunter and Royle in 1924. This episode illustrates excellently the value of painstaking clinical observation. After a great deal of clinical and experimental work, there is still much doubt concerning the major point of their investigation, namely, the influence of sympathetic impulses on muscular spasticity. But two of their incidental observations have opened up important lines of attack in fields quite unrelated to that of their primary objective. Hunter and Royle noted that the obstinate constipation shown by several of their spastic paralytic patients was overcome after lumbar sympathetic ramisection, and also that the foot on the side on

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which operation was performed became much warmer. Operations to interrupt the lumbar sympathetic nerves were then undertaken as empiric procedures by various surgeons in thrombo-angiitis obliterans, Raynaud's disease and Hirschsprung's disease. Dr. Elliott C. Cutler and one of us (Dr. Scott) performed lumbar sympathetic ganglionectomy in two cases of thrombo-angiitis obliterans a few weeks after the visit of Hunter and Royle to this country in 1924. These patients were selected as their symptoms seemed to afford a good basis on which to judge improvement. Both had severe, almost unbearable, nocturnal pain, with the usual manifestations of greatly impaired circulation in the foot. In one case, a large and slowly progressing ulcer on the dorsum of the foot was evidence of serious circulatory deficiency. This patient showed no benefit from sympathectomy and required amputation soon afterward. The other patient showed definite clinical improvement; the paroxysms of excruciating pain were almost entirely controlled, and a gangrenous area on one toe slowly healed. He was able to use his foot for several months, but returned within a year with further gangrene, for which amputation was done. From results of sympathetic interruption reported in the literature, it soon became apparent that some benefit was being achieved in certain cases, while in others the operation failed to affect the disease materially. In fact, this pioneer work has indicated a number of pathologic fields in which sympathetic activity may play a leading rôle in the production of harmful effects. From the first, however, an important obstacle to the clinical exploitation of these possibilities has been the lack of accurate criteria by which to demonstrate and to measure the element of sympathetic activity in the clinical syndromes.

In 1929, this need presented itself to us in deciding on the treatment of a patient with a typical example of Hirschsprung's disease. At that time, the results of interrupting the sympathetic innervation of the large intestine for this condition were recorded in the literature in only seven cases. In five of these, the immediate result was distinctly gratifying, although the interval of postoperative observation was too short to warrant final conclusions. If sympathectomy would cure this patient, we surely wanted to carry it out. On the other hand, if it would not benefit this particular child, we did not want to submit him to the operation unnecessarily. We reasoned that if the abnormality was dependent on activity of the lumbar sympathetic nerves and would be benefited by their removal, then temporary improvement in the motility of the bowel should be demonstrable after the lumbar efferent sympathetic fibers from the cord were paralyzed. Consequently, we determined the motor function of the bowel by a barium enema before and

after the induction of spinal anesthesia.[1] The effect of this procedure was so striking that we were convinced that the patient would be greatly benefited by permanent interruption of the lumbar sympathetic outflow. After bilateral lumbar sympathetic ganglionectomy, the patient began to have regular bowel movements and became capable of completely emptying the contents of the left colon, as demonstrated by a motor test with a barium enema. We have applied this method, with similar convincing results, in another case of Hirschsprung's disease. This procedure has also shown its value in two cases of obstinate constipation not of the Hirschsprung type. The latter patients did not show the rapid emptying of the distended bowel after spinal anesthesia that the former did. We concluded, therefore, that the constipation arose on some basis other than sympathetic activity, and that sympathectomy would not relieve their obstipation. In order to demonstrate further the effect of spinal anesthesia on the motor mechanism of the large bowel, this was studied in the cat. Under the conditions of the experiment, with the animals under light ether anesthesia, the straight intestine was exposed and kept moist with a fine saline spray; it showed no effective peristaltic or expulsive action, even when fully distended with fluid. Shortly after the introduction of procaine hydrochloride intraspinally, vigorous coordinated peristalsis appeared, first in the cecal region, followed in a short time by powerful expulsive contractions, resulting in the emptying of the bowel when it was distended. From this clinical and experimental work, we concluded that spinal anesthesia was a satisfactory method for testing the presence of sympathetic inhibition acting on the large bowel. It also seemed reasonable to expect that this method would prove equally effective in connection with other symptoms under the influence of these nerves. We turned our attention, therefore, to its application in diseases of the peripheral vascular system.

PERIPHERAL VASCULAR DISEASE

REVIEW OF THE LITERATURE

"In those cases of gangrene in which no obstruction has been found after death in the vessels of the dead parts, it is extremely probable that a long persistent spasm of the blood vessels has existed." Thus Brown-Séquard,[2] in a lecture before the Royal College of Surgeons of

1. Roentgenograms of this procedure will be found reproduced in one of our previous papers. Scott, W. J. M., and Morton, J. J.: Sympathetic Inhibition of the Large Intestine in Hirschsprung's Disease, J. Clin. Investigation **9**:247, 1930.

2. Brown-Séquard, C. E.: Course of Lectures on the Physiology and Pathology of the Central Nervous System: Delivered at the Royal College of Surgeons of England in May, 1858, Philadelphia, 1873, p. 148.

England in May, 1858, called attention to the clinical importance of vascular spasm and its differentiation from occlusion. In the early part of the same decade, Claude Bernard had demonstrated the vasoconstrictor fibers in the cervical sympathetic chain. The physiologic action and anatomic pathways of the sympathetic vasoconstrictors are well known. This information, however, has not been applied to the development of a practical method for differentiating the elements of spasm and occlusion, and for determining their relative participation in any individual case of peripheral vascular disease. As will appear later, this distinction is of great significance in the common forms of vascular disease, not merely in the unusual instances, such as those alluded to by Brown-Séquard and those described by Raynaud, in 1862, in his classic monograph on local asphyxia and symmetrical gangrene of the extremities. French investigators,[3] by the use of the oscillometer before and after immersing the extremity in a hot water bath, had attempted this distinction. However, this method gave no index to the blood flow through the finer vessels of the collateral and terminal circulation. It is inadequate for our purposes. The hyperthermia following the parenteral administration of a foreign protein had long ago been advised as a method of treatment in many conditions, among them the peripheral vascular diseases. Brown[4] applied this reaction to the diagnosis of these peripheral vascular diseases, deriving a vasomotor index from a comparison of the increase in surface temperature of the foot with the increase in body temperature. This method offered the first differentiation of spasm and occlusion in the involved area. We have used it several times, but it is disagreeable to the patients and inconvenient to the physician, and in some reported cases[5] has resulted in serious complications. Consequently, we applied ourselves to the development of a simpler procedure to measure the elements of spasm and occlusion in the extremity. It was an obvious step to carry out the same procedure in vascular disease that had been so satisfactory as a test for sympathetic activity in Hirschsprung's disease. We therefore studied the effect of spinal anesthesia on the circulation through the extremities in persons with normal vascular systems as a basis on which to interpret the response in pathologic cases.

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3. Babinski, J., and Heitz, J.: Obliterations artérielles et troubles vasomoteurs d'origine réflex ou centrale, Bull. et mém. Soc. méd. d. hôp. de Paris **40**:570, 1916.

4. Brown, G. E.: The Treatment of Peripheral Vascular Disturbances of the Extremities, J. A. M. A. **87**:379 (Aug. 7) 1926.

5. Allen, A. W., and Smithwick, R. H.: Thrombosis of Peripheral Arteries Following Intravenous Injection of Typhoid Vaccine: Report of Two Cases, New England J. Med. **200**:217, 1929.

METHODS OF MEASURING VASOMOTOR CHANGES IN THE EXTREMITIES

Let us interpose here a few remarks about the method chosen to measure the vasomotor changes in the extremities. Three such methods are available and have been used in studying the peripheral circulation in the laboratory and in the clinic. These are: (1) plethysmographic records of volume changes; (2) determination of the rate of dissipation of heat from the part, usually by a water calorimeter, and (3) determinations of the surface temperature. The plethysmographic and calorimetric methods, though sensitive indexes of the rate of blood flow, are not applicable to comparative determinations in various areas, such as the different toes, or the toe as compared with the sole, etc., data that, as will appear later, are of importance to us. They are available for

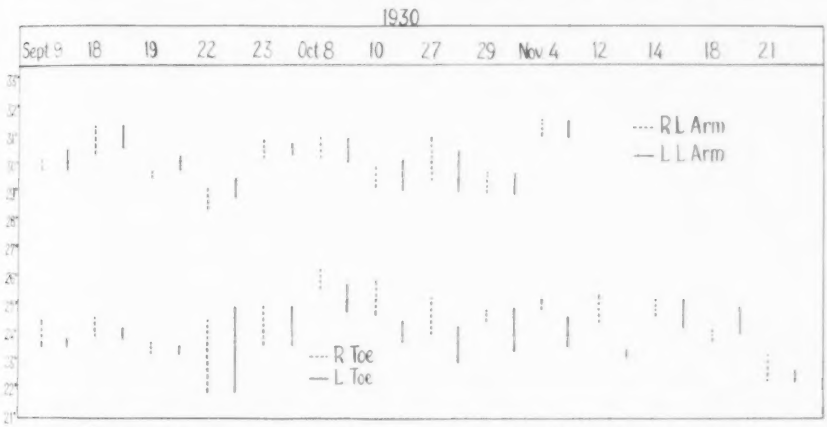

Fig. 1.—Skin temperature variations of a normal subject (Miss O. E.) in a room at a constant temperature (20 C. [68 F.]). Each line represents the maximum and minimum readings over a period of one-half hour. The area of skin was exposed to the standard conditions for fifteen minutes each time before temperature readings were started.

clinical use only when applied to larger parts, such as the whole foot or lower part of the leg. The surface temperature, however, can be easily and quickly determined for any number of points. At a given room temperature, it is an accurate index of the blood flow through the involved area, if this does not closely overlie contracting muscles. In normal persons surface temperatures vary greatly (fig. 1). What, then, is their significance, and how are they of use to us in studying the present problem? The actual reading at which the surface temperature starts is of little significance. It is an index of the arteriolar circulation, which is undergoing many physiologic changes during the day under normal conditions, as is well known. Comparative temperatures

are sometimes of importance, especially when a difference of at least 1 C. (33.4 F.) is shown in symmetrical areas. The chief value of determinations of surface temperature, however, consists in following their response to certain procedures that normally affect the vasomotor activity in the extremity. Thus, if vasoconstriction is well marked, as it normally is or can be induced, in the distal part of the lower extremity, the surface temperature should show a striking increase when the sympathetic vasoconstrictor fibers are paralyzed.

We determined the surface temperatures in a group of persons with apparently normal vascular systems before and after the induction of spinal anesthesia for various types of operations (fig. 2). With the exception of a small group, which we shall presently discuss, all of these

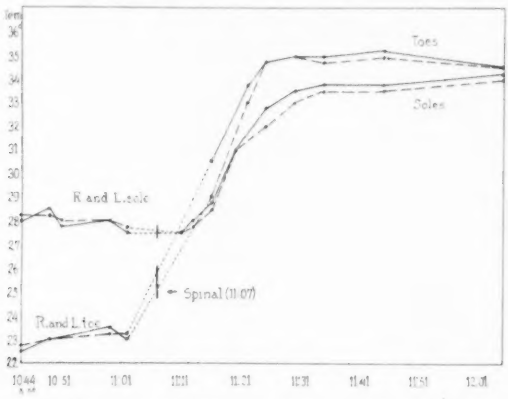

Fig. 2 (case 32599).—Normal response to spinal anesthesia in a case in which herniotomy was performed on the right side (normal blood vessels). Temperatures of toes and soles rise sharply and come to the same level.

patients showed a sharp increase in the surface temperatures of the feet on the establishment of complete anesthesia in that area. After a few observations, it was evident that this furnished a satisfactory basis for demonstrating the presence of vasoconstriction. We later learned that simultaneously in at least two other clinics this same procedure was being developed as a qualitative test for vasoconstriction.[6] After assembling a group of twenty-two such curves in normal persons, a careful study of them yielded further important information. The curves showing a sharp rise in surface temperatures regularly reached

6. White, J. C.: Diagnostic Blocking of Sympathetic Nerves to Extremities with Procaine, J. A. M. A. **94**:1381 (May 3) 1930. Brill, S., and Lawrence, L. B.: Changes in Temperature of the Lower Extremities Following the Induction of Spinal Anesthesia, Proc. Soc. Exper. Biol. & Med. **27**:728, 1930.

a level at which they remained for a considerable time, then gradually declined to approximately the original point (fig. 3). Furthermore, the level that the colder part of the extremity (usually the toes) attained was approximately the same on both sides and also the same as that reached by other parts of the extremity. On comparing this temperature with the original temperature of the warmest part of the exposed body, it was again found to be approximately the same. On studying these results mathematically, we were surprised to find in these twenty-two cases that the height of the temperature attained by the surface of the great toe always fell within 1.5 degrees of the mean. In other words, even without correction for room temperature, which varied considerably in the first series, the skin in these normal extremities became approximately uniformly warmer, not only throughout the extremity,

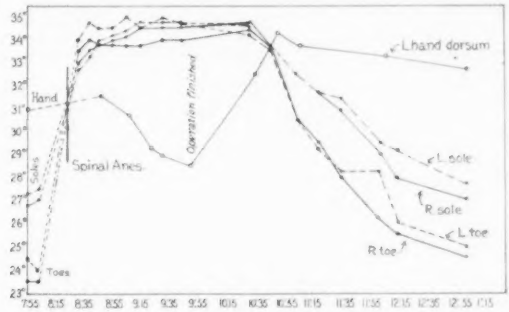

Fig. 3 (W. S. 34172).—A normal vasodilatation level, reached by the toes and soles following spinal anesthesia in a case in which herniotomy was performed, is maintained as long as the complete anesthesia lasts (about two hours). As sensation and motion return to the extremities, the temperatures of the toes and of the soles fall approximately to the point from which they started (reappearance of vasoconstrictor gradient). The hand, not being anesthetized, shows a fall in surface temperature during the operation (psychic and mechanical influences). The room temperature was 24.9 C.

but on comparison of one person with another. We named the level attained the normal vasodilatation level,[7] as it seemed to represent the circulation entirely freed from vasoconstrictor impulses. Three cases were found that did not respond by a sharp rise in surface temperatures after satisfactory spinal anesthesia. In these patients (fig. 4), though the peripheral circulation did not appear grossly abnormal, the skin temperature of the toes and soles started at a very high level, in fact,

7. Morton, J. J., and Scott, W. J. M.: The Measurement of Sympathetic Vasoconstrictor Activity in the Lower Extremities, J. Clin. Investigation **9**:235, 1930.

nearly at the vasodilatation level, and either remained about the same or fell after spinal anesthesia. All three of these patients were markedly cachectic and had advanced carcinoma. Apparently, their condition had already produced a liberation of the peripheral vessels from vasoconstriction. We shall later refer to this same phenomenon in certain vascular diseases. These three cases of carcinoma are examples of Ipsen's narcosis sign,[8] namely, an unfavorable prognosis in persons with presumably normal peripheral blood vessels when the skin temperature in the foot does not rise under general anesthesia. We felt that further information in regard to vasoconstrictor activity could be obtained by studying the effect of other forms of anesthesia. Surgeons have long known that there is a peripheral vasodilatation under general anesthesia. This phenomenon was extensively studied by Ipsen,[9] who used a simple scheme which shows the major changes. We wanted to get further evidence, however, in regard to the level and the mechanism of this

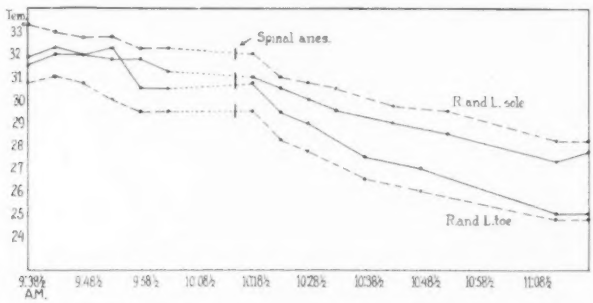

Fig. 4 (case 32374).—Unusual response of normal vessels to spinal anesthesia in a few cachectic persons, as shown in a case of carcinoma of the gallbladder (normal blood vessels). The temperature does not rise after spinal anesthesia, but starts at a high level.

dilatation. Does general anesthesia produce the same complete relaxation of vasoconstriction as that seen following spinal anesthesia? We soon found that nitrogen monoxide-oxygen, ether, and tribromethanol, either alone or in sequence, produced the same characteristic sharp increase in the surface temperatures of the feet that was observed under spinal anesthesia[10] (fig. 5). Also after from twenty minutes to

8. Foged, J.: Ipsen's Narkosephänomen, Deutsche Ztschr. f. Chir. **229**:365, 1930.

9. Ipsen, J.: Les artères et l'anesthésie, Acta chir. Scandinav. **6**:487, 1929.

10. A preliminary report of the effect of general anesthesia on vasoconstriction was given before the Society for Experimental Biology and Medicine. Scott, W. J. M., and Morton, J. J.: Obliteration of Vasoconstrictor Gradient in the Extremities under Nitrous Oxide-Oxygen, Ether, and Tribromethyl Alcohol Anesthesias, Proc. Soc. Exper. Biol. & Med. **27**:945, 1930.

half an hour the elevation of the skin temperature reached and held the normal vasodilatation level. Figure 6 shows how the surface temperatures of the hand, the sole and the plantar surface of the great toe all

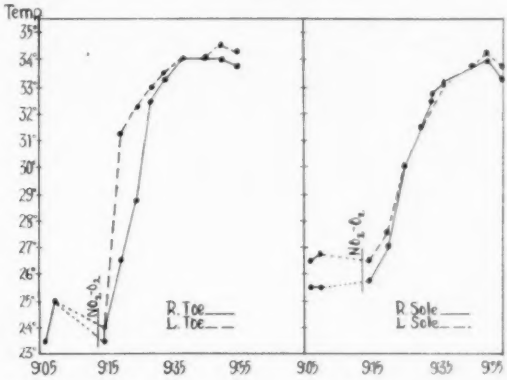

Fig. 5.—Obliteration of normal vasoconstriction by nitrogen monoxide-oxygen in a case in which herniotomy was performed on the right side.

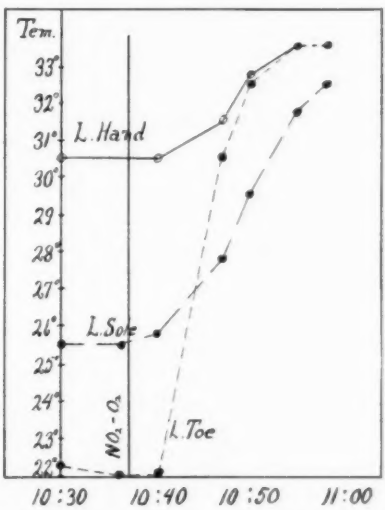

Fig. 6 (case 35082).—Normal vessels. All parts of the extremities come to the normal vasodilatation level (obliteration of the vasoconstrictor gradient).

come to within 1 degree of each other; the vasomotor gradient of the extremity has been obliterated. Furthermore, after this level has been attained either by spinal anesthesia or by one inhalation agent, the addi-

tion of another anesthetic does not alter the surface temperature (figs. 7 and 8). Here there is additional evidence that when once the vasodilatation level is reached, the vessels are devoid of vasoconstrictor influence. There are a few sources of error to avoid in testing for

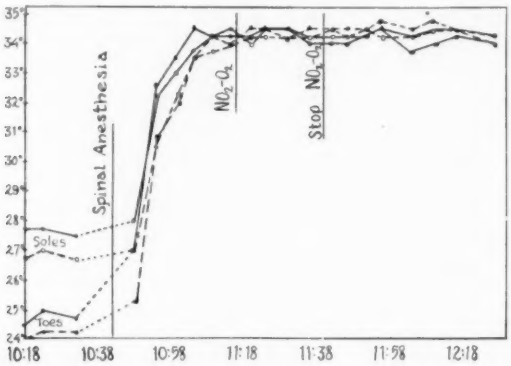

Fig. 7.—When the normal vasodilatation level is obtained by spinal anesthesia, the addition of an inhalation anesthetic produces no further effect, as shown in a case in which exploratory laparotomy and ventral herniotomy were performed.

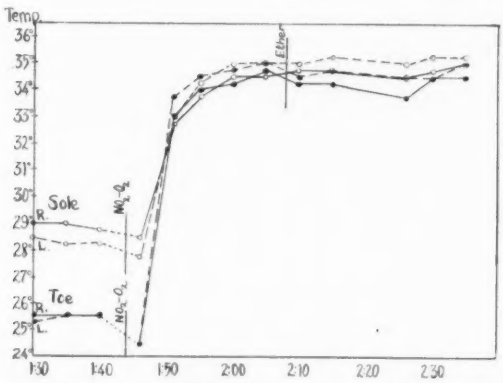

Fig. 8.—When the normal vasodilatation level is obtained by one inhalation anesthetic, the addition of another produces no further effect, as demonstrated in a case in which exploration of the wrist was done.

this normal vasodilatation level. In the first place, the anesthesia in the affected area must be complete if the nerve fibers are blocked chemically (as in spinal anesthesia). In the second place, under general anesthesia a sufficient depth must be attained to provide muscular relaxation (figs. 9 and 10). In the third place, occasionally some local abnormality

of the skin, such as a scar or an extensive callus, will interfere with the normal vascular response at that point. In fact, where the skin is especially thick, the curve of temperature changes is a little slow in rising to its maximum point. Thus, often the temperature of the toe

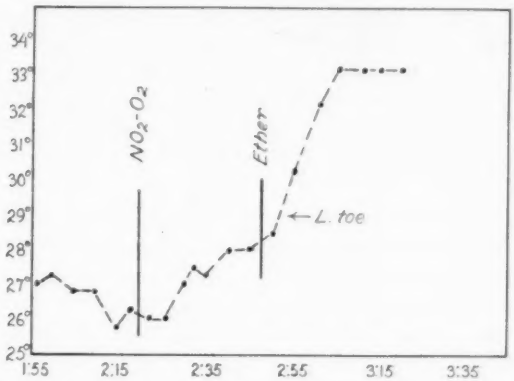

Fig. 9 (S. B. 24432).—Depth of general anesthesia necessary to provide muscular relaxation. Relaxation was not obtained in this case by nitrogen monoxide-oxygen alone. Note the unsatisfactory effect on vasoconstriction. On the addition of ether, with relaxation, note the prompt response of the skin temperatures to the normal vasodilatation level. The room temperature was 25.4 C.

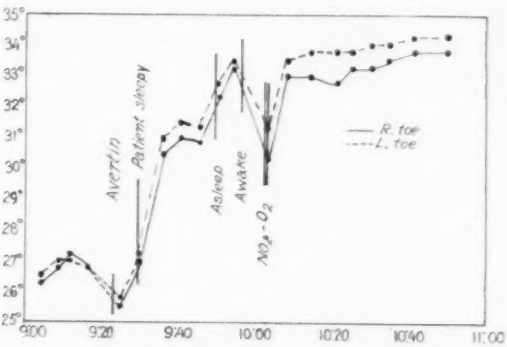

Fig. 10 (C. B. 33971).—Normal vessels; release of vasoconstriction by anesthesia with tribromethanol (in amylene hydrate solution) in a case in which laparotomy was performed for exploration. When the patient was moved to the operating table he awakened, with the recurrence of some vasoconstriction. Nitrogen monoxide-oxygen was then administered, with a prompt return to the vasodilatation level. The room temperature was 25.4 C.

reaches the vasodilatation level more promptly than that of the sole. When the present work was started, the surface temperature was deter-

mined by a mercury thermometer so constructed that the sensitive surface was flat and could be applied to the skin. The bulb of the thermometer was covered with cotton or felt. This method is similar to the procedure that Ipsen used. This was sufficient to give the major swing of the temperature, but did not accurately measure the surface temperature, owing to the retention of heat underneath the felt. The same objection applied also to the usual thermocouple, which took from thirty to forty-five seconds to come to equilibrium. Consequently, a simplified and more sensitive apparatus was perfected, which required about five seconds for each reading.[11] This interval furnishes a true skin temperature determination without the distortion of heat storage under the apparatus.

By avoiding the errors mentioned, we then had two methods either one of which was entirely satisfactory for obliteration of vasoconstrictor activity, namely, spinal anesthesia and general anesthesia. These left nothing to be desired in studying such reactions in any one requiring one of the types of anesthesia for an operation. By this time, however, we had found the test indispensable in the study of any vascular lesion in the extremity. We therefore wished to simplify the procedure so that it could be applied with a minimum of discomfort to ambulatory patients and could be repeated at intervals without inconvenience. It is well established that the sympathetic motor fibers to the vessels of the extremity are segmentally distributed. Weir Mitchell [12] carried out the experiment of temporarily interrupting impulses through a mixed nerve by freezing his own ulnar nerve, and found an immediate increase in temperature in the anesthetized skin field. He also credited Waller with a similar result. Braun,[13] in 1903, emphasized the vasomotor paralysis with hyperemia and hyperthermia limited to the anesthetized area that follows conduction anesthesia. Wiedhopf [14] made an extensive study of this hyperthermia associated with nerve blocking, and advised its use in determining the necessary height for amputation. In fact, he presented evidence suggesting that the vasomotor fibers were more sensitive to the paralyzing action of procaine hydrochloride than the sensory or

11. This apparatus was developed under our direction by the Taylor Instrument Company of Rochester, N. Y. Scott, W. J. M.: An Improved Electrothermal Instrument for Measuring Surface Temperatures, J. A. M. A. **94**:1987 (June 21) 1930.

12. Mitchell, S. Weir: Cases of Lesions of Peripheral Nerve Trunks with Commentaries, Am. J. M. Sc. **86**:17, 1883.

13. Braun, H.: Experimentelle Untersuchungen und Erfahrungen über Leitungsanaesthesie, Arch. f. klin. Chir. **71**:179, 1903.

14. Wiedhopf, Oskar: Experimentelle Untersuchungen über die Wirkung der periarteriellen Sympathectomie und der Nervenvereinigen auf die Gefässe der Extremitäten. Beitr. z. klin. Chir. **130**:399. 1924.

motor fibers. He also advised freezing the nerve trunks in arteriosclerotic gangrene, not only for the relief from pain, but for the dilatation of the arteries, showing that he had not learned to distinguish the spastic and occlusive elements of vascular disease by this method. Lewis and Landis [15] and White [6] suggested the application of this method in the qualitative demonstration of arterial spasm. We first investigated the response of normal persons to such conduction block. Our purpose was to determine how the degree of vasodilatation under such conditions would compare with the normal vasodilatation level previously established. It is obvious that even if all of the vasoconstrictor impulses in the peripheral field are interrupted, on anesthetization of a nerve trunk, vasoconstriction will be present in the larger vessels of

Fig. 11.—Landmarks for posterior tibial nerve block. The nerve is located by palpation and is immobilized with the finger as far distally as it can readily be felt. Injection at this point is distal to the point at which the nerve passes under the posterior tibial artery.

the leg. What proportion of the increase in peripheral circulation seen after spinal and general anesthesia will be obtained under peripheral nerve block? This point required elucidation before the method could be used quantitatively to determine spasm and occlusion in pathologic cases.

In the majority of instances, the problem of peripheral vascular diseases is chiefly concerned with the feet. Consequently, we wished to produce complete anesthesia in a skin area in the most distal part of the

15. Lewis, T., and Landis, E. M.: Some Physiologic Effects of Sympathetic Ganglionectomy in the Human Being and Its Effect in a Case of Raynaud's Malady, Heart **15**:151, 1930.

foot. This was easily obtained by infiltration about the posterior tibial nerve a little below the internal malleolus (fig. 11). The nerve at this point can almost always be felt after it has passed under the posterior tibial artery. If procaine hydrochloride is infiltrated into this region, conduction block anesthesia of the corresponding skin field involves most of the sole and the plantar surfaces of the heel and of all of the toes. This procedure was carried out in sixteen persons (medical students) with normal blood vessels, and it was found that the same form of curve was obtained in the anesthetized area that ensued after spinal or

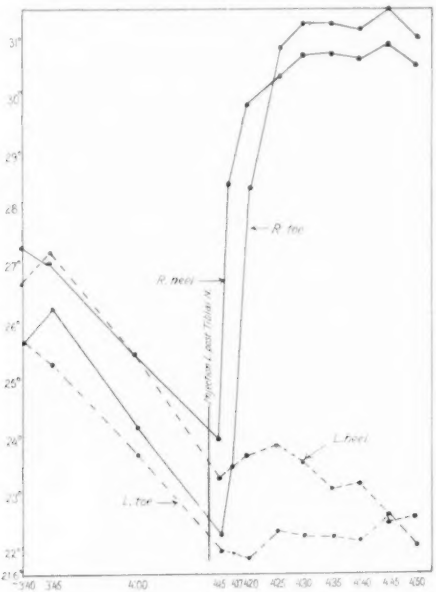

Fig. 12.—Normal vessels showing vasodilatation obtained following conduction block of the left posterior tibial nerve in R. W. The temperature of the room was 20 C.

general anesthesia (fig. 12). Under standard conditions, the height of the curve in these normal persons came within a range of 1.5 degrees, but the mean of the maximum temperatures obtained under conduction block was about 1 degree below that obtained under spinal or general anesthesia. Consequently, it seemed clear that in the involved area all but a small fraction of the increased circulation that follows spinal and general anesthesia was obtained by blocking the vasoconstrictor fibers in the nerve trunk only a few inches from the peripheral field. In order to verify this, the maximum surface temperature readings of

the foot of the same person were compared following conduction block of the posterior tibial nerve with those obtained shortly thereafter under general anesthesia (fig. 13). The skin temperature of the great toe reached its height at 32.9 C. (91.2 F.) under the nerve block, while its maximum under nitrogen monoxide-oxygen and ether anesthesia was 33.6 C. (92.5 F.). It is apparent, then, that conduction block is a satisfactory method of estimating vasoconstriction, though in borderline pathologic cases it is probably desirable to check the data so obtained with the result of either spinal or general anesthesia.

We have shown the effect on the surface temperatures of the extremities of the temporary abolishment of vasoconstriction by three

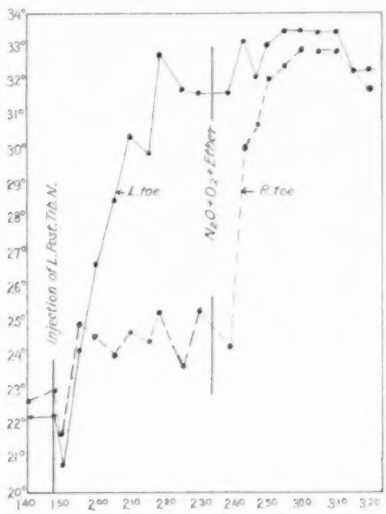

Fig. 13.—Normal vessels; comparison of vasodilatation obtained by blocking the left posterior tibial nerve with that following inhalation anesthesia in J. J. The temperature of the room was 22 C.

different methods, and have established the normal vasodilatation level by these procedures as follows: at a room temperature of 20 C. (68 F.), the surface temperature of the great toe reaches at least 31.5 C. (88.7 F.) with general or spinal anesthesia and 30.5 C. (86.9 F.) with nerve block of the posterior tibial nerve. (If the determination is carried out in a warmer room, a correction factor of 0.3 C. [32.5 F.] should be added to these levels for each degree centigrade by which the room temperature exceeds 20 C.). By comparing the effect obtained in pathologic cases with these figures for the normal response, we are

now able to divide all peripheral vascular disturbances in the extremities into three main categories. The circulatory symptoms in the respective groups are due to: (1) occlusion alone, (2) spasm alone and (3) mixed spasm and occlusion. Most cases of endarteritis obliterans, whether of diabetic or of arteriosclerotic origin, fall into the first group of occlusion alone (figs. 14 to 17). Probably most cases of Raynaud's disease and many of the cases that have been classified as thrombo-angiitis obliterans respond in their earlier stages to anesthetization of the vasoconstrictor fibers with a dilatation to the normal level (figs. 18 to 20). Many examples of thrombo-angiitis obliterans and also some of syphilitic arteritis show both spasm and occlusion by this test (figs. 21 and 22).

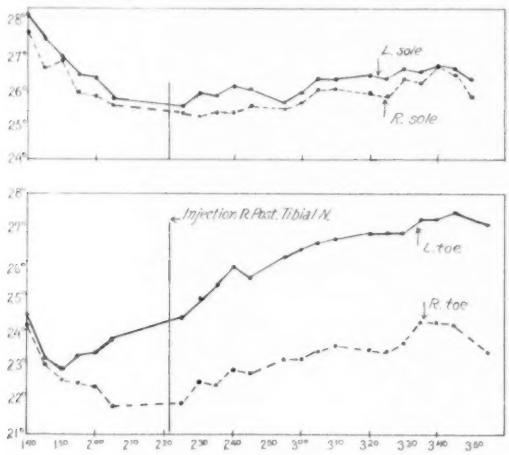

Fig. 14.—Endarteritis obliterans in C. W. No palpable pulses in either foot. Right toes show marked dependent rubor. Gangrene threatened on the right, not on the left. Injection of the right posterior tibial nerve causes no significant increase in temperatures. Gradual increase in surface temperature of left toe occurs on the unanesthetized side. Interpretation: circulatory deficiency in right foot due to occlusion without spasm. Room temperature was 20 C.

In the first group (occlusion), with the establishment of a satisfactory anesthesia by any of the three methods outlined, there is practically no increase in the surface temperature of the involved part. Frequently, the most distal part of the extremity will show this type of response, while a small amount of vasoconstriction can still be demonstrated in more proximal areas. The second group (spasm) includes many examples in which the history strongly suggests a spastic lesion by the extreme variation of symptoms during different periods. This is, of course, particularly well exemplified by the white and blue phases of

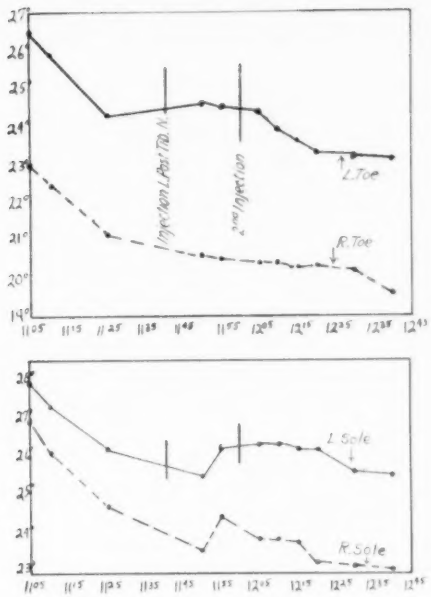

Fig. 15.—Endarteritis obliterans in a man, aged 41. Circulation in the left foot dangerously impaired, with a small indolent ulcer on the dorsal surface of the left great toe. Conduction block of left posterior tibial nerve was not followed by increase in temperature, indicating occlusion without spasm. Temperature of the room was 21.1 C.

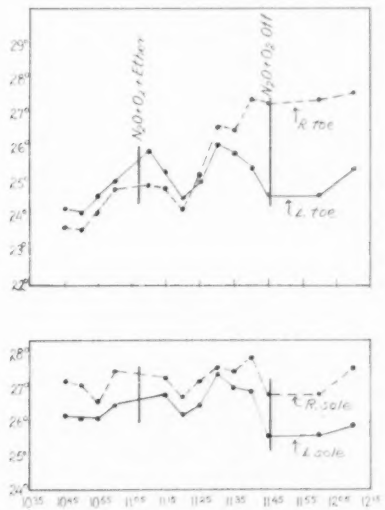

Fig. 16.—Diabetic endarteritis obliterans in Mr. E. S. No increase in surface temperature of the left toes; those on the right show very slight increase with an occlusion index of 5 C. The temperature of the room was 21.1 C.

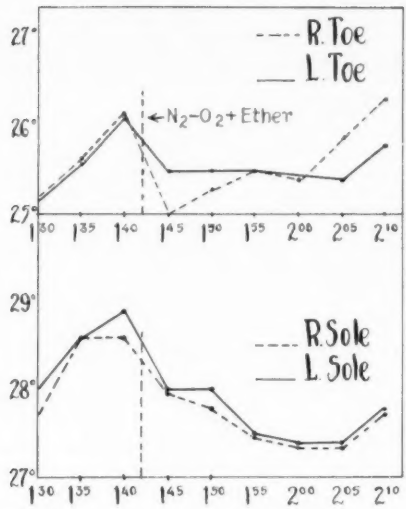

Fig. 17 (case 6756).—Diabetic endarteritis obliterans. No increase in surface temperature after inhalation anesthesia. Occlusion without spasm. Temperature of the room was 21.1 C.

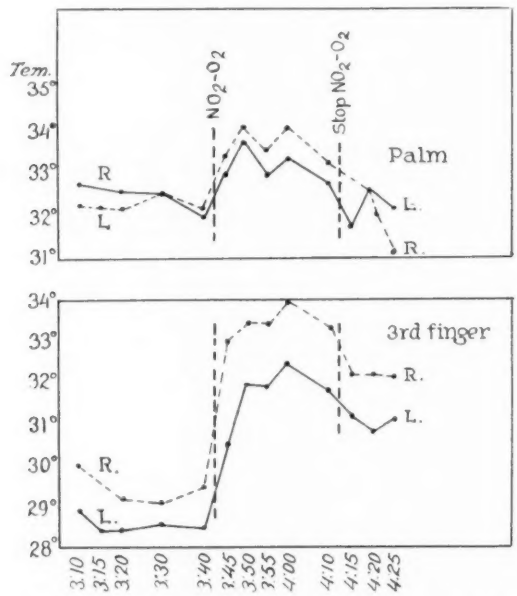

Fig. 18.—Angiospasm of the hands (Raynaud's type). Following inhalation anesthesia, the right third finger reaches the vasodilatation level. The left shows a marked increase, but remains nearly 2 degrees below the right, showing a slight occlusion index in the left third finger. This corresponds with the clinical picture, as there had been a superficial area of necrosis on the left third finger, leaving a scar.

Raynaud's disease, with intervening periods of normal color and apparently normal circulation. But many times it is found that spasm is the outstanding cause of symptoms in cases of common vascular diseases that appear clinically exactly like the outspoken members of the occlusion group. A large number of the presenile vascular diseases show both spasm and occlusion. Obviously, there are many degrees in the exact proportion of each of these two elements in the various cases. Some show a mere trace of spasm still present, while others attain almost the normal levels after anesthesia. To designate the proportions of spasm

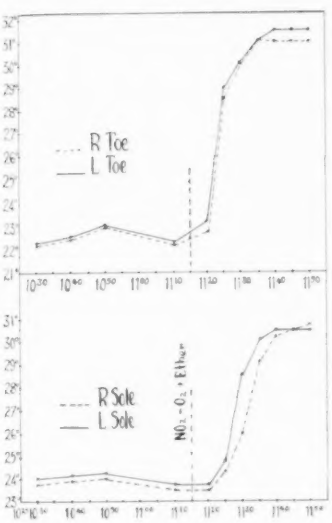

Figure 19

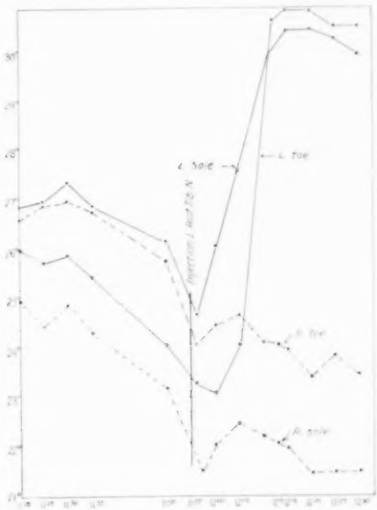

Figure 20

Fig. 19 (case 42685).—"Diabetic endarteritis obliterans," clinical diagnosis. Circulatory impairment causes pain and disability, more severe on the right. Test with inhalation anesthetic shows circulatory symptoms chiefly due to spasm. Occlusion index about 1 C. The room temperature was 22.7 C.

Fig. 20.—Same effect shown by conduction block of left posterior tibial nerve in a case of arteriospasm in F. C. S. Compare the heights of the temperatures obtained under nerve block and inhalation anesthesias. Temperature of the room was 20 C.

and occlusion in any area, the highest surface temperature (centigrade) attained is subtracted from the lowest normal reading established for the type of anesthesia used. This figure is called the occlusion index and is of importance in determining the type of treatment to be adopted in the mixed group. We may emphasize here the fact that

these clinical groups are established on the basis of their physiologic response rather than on a pathologico-anatomic basis. Probably a certain amount of organic occlusion caused by thrombosis or by narrowing of the lumen is present in nearly all of the cases of vascular disease,

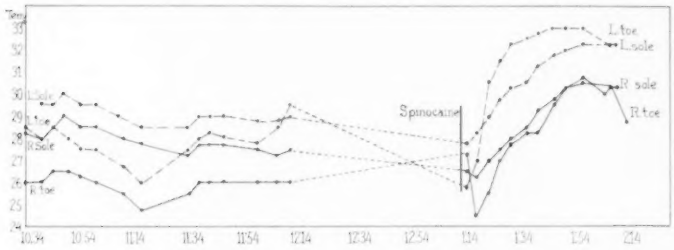

Fig. 21 (case 31391).—Syphilitic endarteritis obliterans. No pulsations in the right foot and feeble pulsations in the left. Circulation seriously impaired on the right. Following spinal anesthesia left foot comes up to the normal vasodilatation level. Right foot shows a definite but incomplete rise with an occlusion index of 2.5 C.

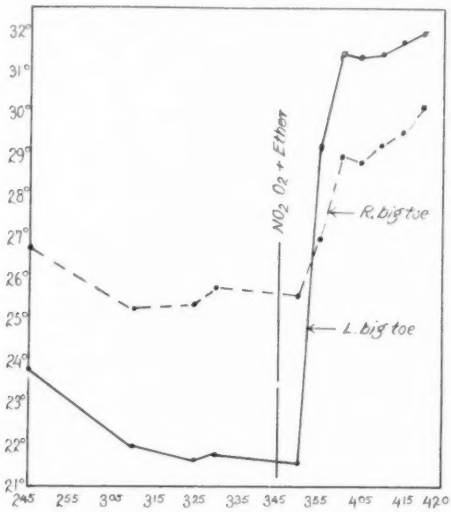

Fig. 22.—Thrombo-angiitis obliterans with migratory phlebitis in P. B. Symptoms at present limited to the right. Inhalation anesthesia shows response on the left to the normal vasodilatation level; on the right, a definite but incomplete rise. Occlusion index, 2 C. Temperature of the room was 21 C.

with the exception of the earlier stages of Raynaud's disease. But there is an important difference in the effect of such changes on the

circulation of the foot, primarily owing to the behavior of the collateral and terminal vessels. The location of these important arteries is visualized in the accompanying roentgenograms. Figure 23 shows an intra vitam injection of the arterial tree with an iodine salt. An obstruction in the posterior tibial artery is seen; the small anastomotic branches running parallel to the main vessel can be followed down to

Fig. 23.—Arteriosclerosis with occlusion of posterior tibial artery; intra vitam injection. This figure is shown to illustrate the collateral circulation through the small vessels. The posterior tibial artery blocked in about the middle of the calf is reconstituted opposite the malleolus (retouched photograph).

the point where the channel is reconstituted in the main artery about opposite the internal malleolus. Figure 24 shows an injected specimen of a leg amputated on account of infection. It shows very nicely the smaller terminal arteries in the foot. In advanced noninflammatory occlusive disease, such as that typically seen in arteriosclerosis or diabetic endarteritis, vasoconstriction, even that amount usually present in nor-

mal persons, is lacking. Apparently some compensatory mechanism has released the anastomotic and terminal arteries and arterioles from all vasoconstrictor effects (figs. 25 and 26). It is exactly thus that vascular disease associated with spasm differs from the occlusive form. In advanced stages of arteriospasm threatening the viability of the part,

Fig. 24.—Injection of amputated extremity to illustrate the terminal finer arteries. Note the occlusion of the posterior tibial artery in the lower third of the leg shown between the tibia and fibula. The viability of the foot is more dependent on the anastomotic and terminal arteries and arterioles than on the main arteries in the lower leg.

vasoconstriction still persists and is not released by the compensatory mechanism seen in the occlusive group. What causes this difference? We do not yet have final proof, but it is our hypothesis that the inflam-

matory reaction extending through the wall of the vessels, which is so characteristic pathologically of thrombo-angiitis obliterans, affects the afferent nerve fibers in the adventitial coat or even in the accompanying nerves themselves. This sets up a reflex vasoconstrictor spasm, the particular importance of which is that it involves not only the diseased main arteries, but the collateral and terminal small vessels in the periphery. Consequently, when the circulatory deficit reaches a certain

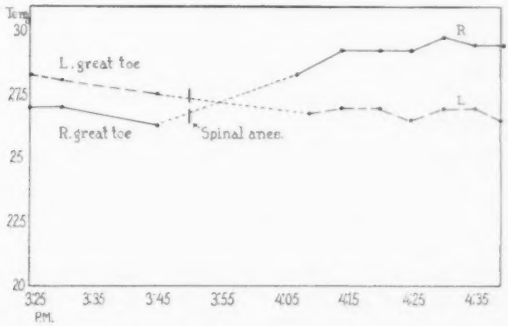

Fig. 25 (case 31766).—Endarteritis obliterans on the left. No pulsation on the left, feeble on the right. Circulation of left foot dangerously impaired. Left great toe shows no rise after spinal anesthesia, right great toe shows slight increase. Note that the side with the more seriously involved peripheral circulation starts at a higher level and shows no vasoconstriction, while the less involved side shows a slight amount of vasoconstriction still present.

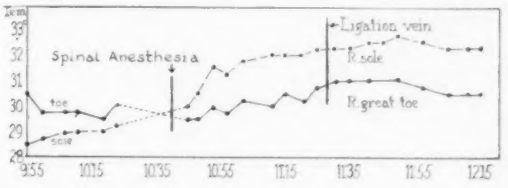

Fig. 26 (case 26956).—Diabetic endarteritis obliterans (arteriosclerotic vessels). Left leg amputated previously. Circulation in right toes seriously impaired. Following spinal anesthesia, no increase in surface temperature of the toes, but definite increase in the sole. Note particularly the reversal of the normal vasoconstrictor gradient, with the temperature of the toe starting at a higher initial level than that of the sole, owing to the absence of vasoconstriction in the toe.

point in occlusion it brings into play the compensatory release of normal vasoconstriction, but in the spastic group this reflex vasoconstriction continues. We have found that in vascular disease the efficiency of the circulation to the distal part of the extremity is much more dependent

on these smaller arteries than it is on the main arterial trunk. An illustration of this is found in a case of arteriosclerotic endarteritis in which there was diminution or absence of pulsation in all four major vessels of both feet. However, the left dorsalis pedis artery could barely be felt; the right was not palpable. This greater impairment of the large vessels in the lower part of the right leg was borne out by the following oscillometric readings: On the left side, the swing was one and one-half major divisions, while on the right side it was only one-half. Yet in spite of the more complete occlusion of the larger arteries, the temperatures of the right toes were 1 degree higher than those of the left, showing a more rapid peripheral circulation on the side with the more defective major arteries. This phenomenon was probably due to the fact that the left side was still affected by vasoconstriction, while on the right side the compensatory mechanism had released it.

A review of the relationship of sympathetic stimuli to peripheral blood vessels shows a varying degree of vasoconstrictor activity in the normal person. In occlusive disease without inflammatory reaction in the outer wall of the blood vessels, this normal vasoconstriction is released when the circulation becomes seriously impaired. In spastic disease, vasoconstriction continues even when the reduced circulation to the part endangers its viability. When some of the anastomotic and terminal vessels become occluded also, the mixed type results. There are many more examples of spasm among the common diseases of the peripheral blood vessels than is usually realized.

TREATMENT

The differentiation of occlusive and spastic vascular disease and the estimation of the relative proportions of each when both are present are of prime importance, because the principles on which the treatment for these groups must rest differ radically (fig. 27). In the group in which symptoms are entirely dependent on occlusion, nothing whatever is gained by the elimination of vasoconstrictor activity. Sympathectomy for such patients is unjustifiable. Besides symptomatic relief from discomfort and the avoidance of infection, treatment should be directed to one end, namely, a more efficient peripheral distribution of the blood. Venous ligation seems to offer some assistance in this direction. It is probably in this manner also that pain in such cases may be somewhat alleviated by depression of the level of the feet, gravity thereby being used to assist in the forcing of blood through the most distal parts. It is not our purpose to discuss extensively the treatment for occlusion. We want particularly to emphasize that there is no evidence of participation of the sympathetic activity in this group. On the other hand, in conditions in which spasm is present the treatment is entirely different

and should consist in measures to overcome the spasm. There are several ways in which this problem may be attacked.

1. *Overcoming the Inflammatory Process.*—The most direct and satisfactory procedure would be to overcome the inflammatory process. In syphilitic vascular disease this can sometimes be achieved, and the possibility of this specific agency being the cause of the condition should always be considered, particularly in the mixed group showing both spasm and occlusion. It is our impression from the limited number of examples of syphilitic arteritis in which we have tested for spasm that spasm was mixed with some occlusion and was not usually an especially striking phenomenon. In the arterial spasm of thrombo-angiitis obliterans and Raynaud's disease, we do not yet know the primary cause of

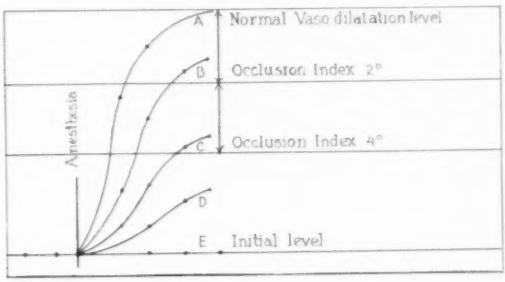

Fig. 27.—Response to anesthesia as a guide to treatment. If the surface temperature rises to the normal vasodilatation level, curve *A*, or to within 2 C. (35.3 F.) of this point (occlusion index less than 2 C.), curve *B*, the treatment should be directed toward overcoming the spasm. If the rise in temperature is definite with an occlusion index between 2 and 4 C. (39.1 F.), curve *C*, the release of spasm may be of assistance. But if the rise in surface temperature is only to a point at which the occlusion index is more than 4 C., curve *D*, or if there is no rise, curve *E*, treatment should be for occlusion; sympathectomy is unjustifiable.

the reaction. Any information along this line will be gratefully received by all who are required to treat patients with vascular diseases in the extremity.

2. *Vasodilator Drugs.*—It is natural next to turn for assistance to the pharmacologic agents that cause vasodilatation or oppose sympathetic stimulation. We have tried out in this connection the nitrites, acetyl choline and ergotamine, but we have not been able to obtain an immediate effect on the peripheral vessels of the extremity in arterial spastic disease that at all approaches the interruption of the sympathetic fibers.

3. *Local Heat.*—In certain forms of arterial spasm, heat applied locally relaxes the spasm. This is particularly true in certain traumatic lesions. It is impossible to use readings of the surface temperature

directly as an index of the effect of local heat on the vascular circulation. We have studied in isolated instances the normal recovery from heat and cold, but have not yet established satisfactory criteria for the normal limits. The effect of local heat in arterial spastic disease is not as lasting as the application of heat to raise the body temperature.

4. *General Heat.*—We have produced hyperthermia in these patients by two methods: (*a*) diathermy and (*b*) hot baths. Dr. S. L. Warren supervised the diathermy treatments, which consisted in the passage of 5 amperes of high frequency current (wavelength 300 meters) through

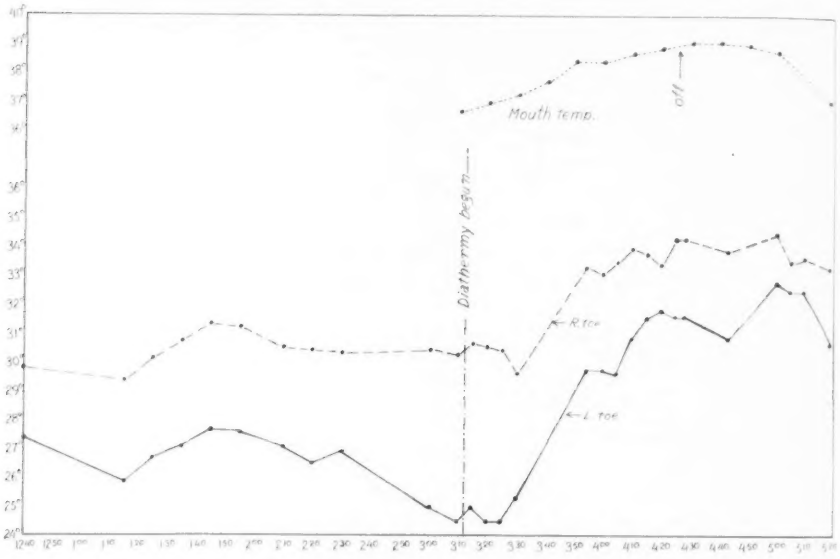

Fig. 28.—Arteriospasm, the effect of diathermy in Mr. C. B. Sympathectomy had been performed on the right side. Diathermy caused a rise in the mouth temperature and the surface temperature of the denervated side, but a much greater rise proportionately on the side not operated on. A difference of over 5 C. (41 F.) in the skin temperature of the two toes recorded at the beginning of treatment is reduced to 1 C. (33.4 F.). Note also that the surface temperature of the left toe is still elevated considerably above its initial point after the mouth temperature had returned to normal. Temperature of the room was 22 C.

the body between large electrodes. The continuous hot baths were given by the method recently advised by Mehrtens and Pouppirt.[16] In our cases both procedures caused a relaxation from arterial spasm which outlasted the hyperthermia produced (figs. 28, 29 and 30). Pain was temporarily alleviated. We have not yet followed these patients long

16. Mehrtens, H. G., and Pouppirt, P. S.: Treatment of Intermittent Claudication with Hyperpyrexia Produced by Baths, J. A. M. A. **95**:1910 (Dec. 20) 1930.

enough to determine how effective these measures will prove in permanently keeping the spasm under control. We believe, however, that they produce a much more desirable form of hyperthermia than that following foreign protein.

5. *Foreign Protein.*—The injection of various types of foreign protein has long been used in the treatment for several conditions, among them the peripheral vascular diseases. Allen and Smithwick [17] and Brown and Henderson [18] have found considerable improvement following repeated injections of typhoid vaccine. The former workers have

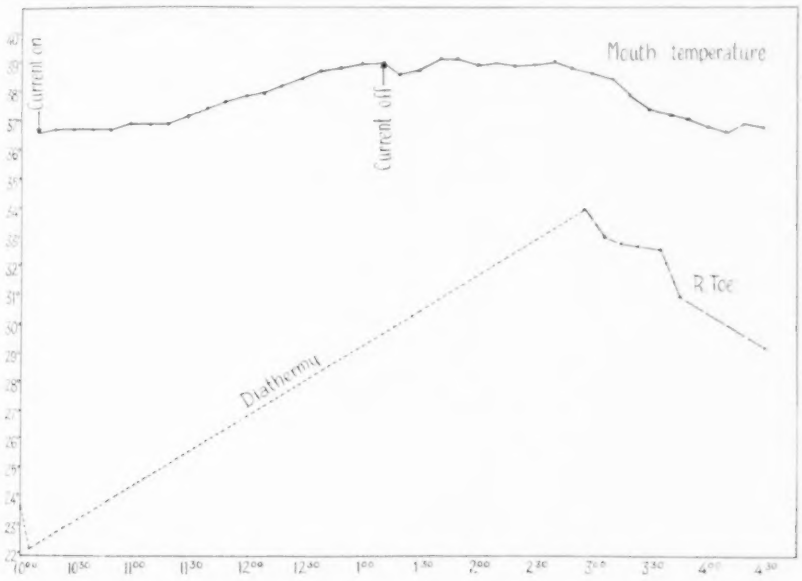

Fig. 29.—Arteriospasm the effect of diathermy in Mr. F. S. Note that the surface temperature in the toes is still elevated three hours after the diathermy was discontinued and after the mouth temperature had returned to normal. Temperature of the room was 25 C.

called attention to the danger of thrombosis with this method.[5] Even though the effect may prove somewhat more persistent than that following hyperthermia produced by the methods already described, the

17. Allen, A. W., and Smithwick, R. H.: Use of Foreign Protein in Treatment of Peripheral Vascular Diseases: Results of Intravenous Injections of Typhoid Vaccine, J. A. M. A. **91**:1161 (Oct. 20) 1928.

18. Brown, G. E., and Henderson, M. S.: The Diagnosis and Treatment of Arterial Vascular Disease of the Extremities, J. Bone & Joint Surg. **9**:613, 1927.

severity of reactions, whether or not associated with complications, makes it not an ideal form of treatment.

6. *Surgical Interruption of Sympathetic Fibers.*—Whenever vasoconstriction is demonstrated, it can be overcome by the interruption of the sympathetic fibers to the involved area. This may be done at different levels. The first attempt to accomplish this was periarterial sympathectomy. Leriche developed the procedure of denervating a length of artery by the removal of its adventitia. He thought that

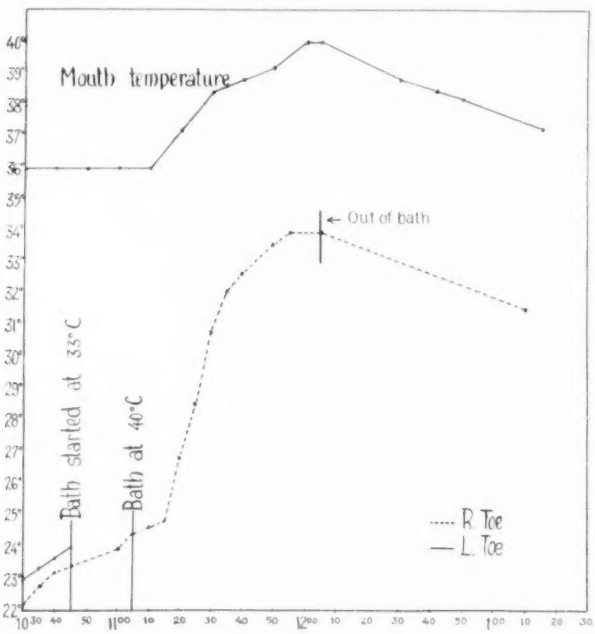

Fig. 30.—Arteriospasm the effect of a continuous hot bath in Mr. F. S. Note the more rapid fall in mouth temperature than in surface temperature after the completion of the bath. Temperature of the room was 22.7 C.

thereby he interrupted efferent fibers to the peripheral field. Following this procedure it was reported that a vasodilatation occurred in the corresponding extremity. Later it was added that vasodilatation also occurred in other extremities, which was thought to be due to some type of reflex disturbance. More recently anatomic studies have verified the previous anatomic and physiologic conception that the vasoconstrictor fibers for distant fields are confined to the main nerve trunks. A study of the surface temperatures in the extremities after other simple operations, such as herniotomy, shows that some of these vascular

changes previously thought due to interruption of sympathetic fibers are merely nonspecific postoperative effects (fig. 31). Possibly some of the results reported are due to interruption of afferent fibers. Under any circumstance, it is quite clear that periarterial sympathectomy is not a satisfactory method of overcoming vasoconstrictor spasm in the extremities.

7. Ganglionectomy.—Approximately the same degree of vasodilatation that can be temporarily induced by anesthesia can be made permanent by sympathetic ganglionectomy in the proper area. The duration of the effect has been questioned. We have patients now that have maintained for more than two years a constant elevation to a

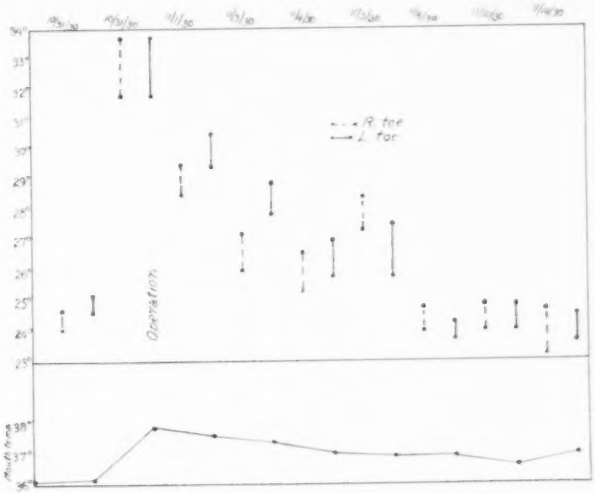

Fig. 31.—Nonspecific postoperative effect on peripheral circulation of normal vessels in C. M., on whom herniotomy had been performed on the right side. Each line represents the maximum and minimum temperatures recorded under standard conditions (room temperature 20 C.) for a period of one-half hour each day. Note the marked elevation above the original level for several days following herniotomy under local anesthesia.

high level on the side on which operation was performed (figs. 32 and 33). Brown and Adson,[19] Filatov[20] and others reported similar

19. Brown, G. E., and Adson, A. W.: Physiologic Effects of Thoracic and of Lumbar Sympathetic Ganglionectomy or Section of the Trunk, Arch. Neurol. & Psychiat. **22**:322 (Aug.) 1929.

20. Filatov, A.: Klinische und experimentelle Untersuchungen über die Schwankungen der Hauttemperatur nach chirurgischen Eingriffen am lumbalen und cervicalen Abschnitte des sympathischen Nervensystems, Beitr. z. klin. Chir. **149**:95, 1930.

effects, some over even a longer period. The influence of sympathectomy on the progress of the thrombotic process in the mixed group, as in certain cases of thrombo-angiitis obliterans, is not known as yet. It is our belief that not only will the circulation be relieved of the spastic

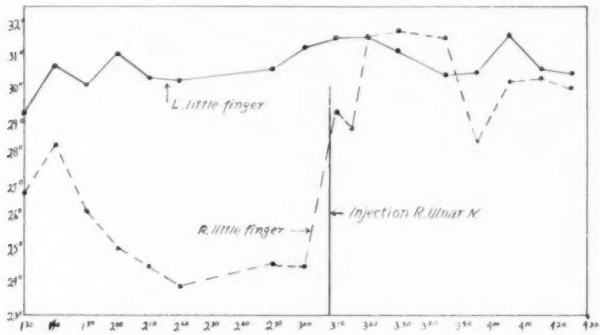

Fig. 32.—Left cervical sympathectomy three months previous to test in Miss L. D. Surface temperature of the left fingers was maintained at a high level, which is the same level reached by the right little finger after the right ulnar nerve was blocked with procaine hydrochloride. Temperature of the room was 20.5 C.

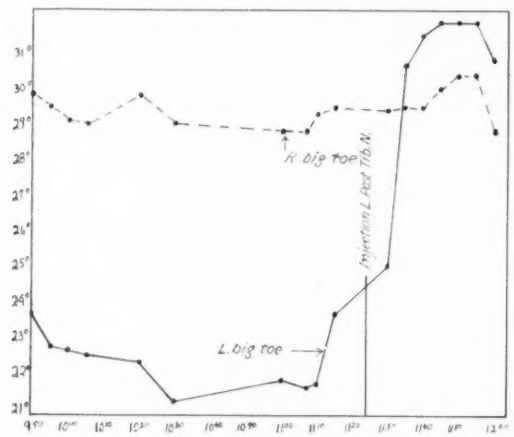

Fig. 33.—Thrombo-angiitis obliterans twenty months after right lumbar sympathectomy in P. B. Surface temperatures on the right side have been maintained at a high level continuously since operation (for twenty months when this paper was written), together with great improvement in symptoms on this side. The level maintained is a little below that reached by the left great toe after the left posterior tibial nerve was blocked with procaine hydrochloride. Temperature of the room was 20 C.

element, but the absence of spasm may exert a beneficial effect to retard extension of the thrombosis. Our opinion in this matter is based on the known development of thrombosis as a complication of the arterial spasm in the later stages of Raynaud's disease. It is also influenced by the possibility that reflex spasm of the vasa vasorum may be a factor in an extension of the disease. These considerations in regard to the further progress of the thrombotic element are at present theoretical; the effect of ganglionectomy in improving the peripheral circulation by removing arterial spasm is proved.

In some cases, particularly those in which pain is an important element in the disease, as Smithwick and White [21] have pointed out, interruption of the peripheral nerve may be of benefit to overcome the pain and to release the arterial spasm in the peripheral area supplied. This is particularly applicable to older persons who should not be submitted to ganglionectomy and in cases in which hyperthermia by physical means is not advisable or proves insufficient. We have recently used alcohol injection into the peripheral nerve with great satisfaction in overcoming the painful excessive reaction to moderate cold in a case of causalgia.

In the mixed group, we do not yet have a sufficiently extensive experience to decide definitely the proportion of occlusion beyond which the results do not justify sympathectomy. As a tentative plan, we are not doing this operation if the occlusion index is over 4 degrees in the foot. We have seen improvement in the circulation of the foot after sympathetic denervation, with the progression of the thrombotic process in one or two toes to the point that local amputation of the latter was necessary. This we did not consider a reflection on the desirability of the sympathectomy.

In brief, as long as spasm is the dominant factor in the viability of the extremity, measures are mainly directed toward the overcoming of this vasoconstriction. We know that surgical interruption of the sympathetic fibers will effect this result promptly. Certain simpler methods, however, also do so temporarily. The exact value of the latter must be worked out by extensive studies. At present, the choice between conservative measures and an operation on the sympathetic system must be decided in each case separately. If spasm cannot be controlled by other measures, sympathetic ganglionectomy may be less radical than nonoperative treatment.

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21. Smithwick, R. H., and White, J. C.: Elimination of Pain in Obliterative Vascular Disease of the Lower Extremity (A Technique for Alcohol Injection of the Sensory Nerves of the Lower Leg), Surg., Gynec. & Obst. **51**:394, 1930.

COMMENT

This study of the sympathetic influence on the vascular system has brought to light a fundamental difference in the control of the peripheral and the splanchnic arteries. The usual surgical depth of general anesthesia entirely obliterates vasoconstriction in the extremities, while it scarcely affects that of the splanchnic area. This seems to be dependent on an anatomic or, more probably, a phylogenetic difference in the vasomotor control for these regions.

In the future, data based on this distinction of spasm and occlusion and a more minute study of these elements will greatly assist in settling many fundamental questions concerning peripheral vascular diseases. When and how in the occlusive group does obliteration of normal vasoconstriction occur? How does the arteriospasm of the spastic group differ from normal vasoconstriction: in severity, in persistence or in what way?

SUMMARY

Pioneers have recently opened up important possibilities in the application of anatomic and physiologic knowledge of the sympathetic nervous system to several clinical syndromes. For the achievement of sound progress in this interesting field there is now needed the establishment of criteria by which to measure the sympathetic activity in the various systems. The effect of the temporary interruption of the extrinsic nerve supply to the large bowel by spinal anesthesia is offered as an index of the amount of sympathetic inhibition present in megalocolon. For vascular diseases of the extremities, a simple, systematic test is outlined which distinguishes the effects of spasm and of occlusion. The vasoconstrictor stimuli to the area studied are interrupted by anesthesia, the effect of which on the surface temperature is compared with the similar response of normal persons. We have established the normal levels for spinal, general and conduction block anesthesia. In an individual case, if anesthesia is accompanied by no elevation of temperature in the cool distal part of the extremity, occlusion without spasm is present; if the skin temperature reaches the normal vasodilatation level, sympathetic vasoconstriction is responsible for the circulatory symptoms, and if the elevation is definite but not to this level, both occlusion and spasm participiate. The difference between the highest temperature obtained and the normal vasodilatation level has been termed the occlusion index, as it measures the effect of organic obstruction to the peripheral circulation. Nerve block anesthesia is particularly useful in this vasomotor test on account of its simplicity and freedom from discomfort. In doubtful or borderline cases, its results should be checked with those of spinal or general anesthesia.

By these methods, valuable information in regard to the nature and the treatment of various types of vascular disease in the extremities is obtained. In the purely occlusive group some compensatory mechanism releases the collateral and terminal vessels from vasoconstriction when the local circulation is seriously reduced. This does not obtain in the spastic group.

The treatment for these two groups should be along radically different lines. The principle of that for purely occlusive disease is the obtaining of a more peripheral distribution of the reduced amount of blood available, while in spastic disease the treatment should be directed toward an augmentation of the local circulation by overcoming sympathetic vasoconstrictor spasm. Particularly valuable methods are hyperthermia, which produces temporary vasodilatation, sympathetic ganglionectomy for permanent effects and interruption of the peripheral nerves in cases in which ganglionectomy is desirable but contraindicated by the patient's condition.

ELECTROCARDIOGRAPHIC STUDIES OF THE EFFECT OF ANAPHYLAXIS ON THE CARDIAC MECHANISM*

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The present conception of anaphylaxis indicates that symptoms and death occur as the result of the mechanical irritation produced on the cells of the so-called shock organ by the interaction of antigen and antibody. This shock organ has been shown to differ with various animals. Thus, in the guinea-pig, it has been found to be the smooth muscle of the bronchi and bronchioles. A guinea-pig dying in anaphylactic shock presents a definite and characteristic group of symptoms, the most prominent of which is gasping for breath. The animal dies with its lungs in a state of maximal distention. These symptoms are due to a closure of the bronchi and bronchioles, so that while air may be taken into the lungs because the accessory muscles of respiration are brought into play, it cannot be forced out of the lungs. The guinea-pig, therefore, dies in acute asphyxia. In the rabbit, however, the shock organ is the media of the arterioles. In cases in which the fatal dose of protein is given in the vein of the ear of a sensitive rabbit, the first arterioles to be affected by the interaction of this protein (antigen) and the antibody are those of the pulmonary system. This interaction brings about irritation with subsequent constriction of these vessels followed by obstruction to the flow of blood through them and to the lung. The result is obvious: lack of aeration of blood and, therefore, asphyxia; damming back of the blood into the right side of the heart with subsequent dilatation of that side, and congestive heart failure if death is delayed.

While the mechanism of anaphylactic shock in the guinea-pig and in the rabbit is fairly well understood, there is but little in the literature with regard to the series of changes occurring in the heart during anaphylaxis, particularly with reference to the disturbances in the cardiac mechanism. In 1910, by direct and graphic observations, Auer and Lewis [1] showed that various disturbances in conduction take place in

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1. Auer, J., and Lewis, P. A.: Anaphylaxis in the Guinea Pig. J. Exper. Med. **12**:171, 1910. (Plate IX, figure 5).

the guinea-pig during anaphylaxis. Königsfeld and Oppenheimer [2] carried this study further and demonstrated practically the same thing with the electrocardiograph, but they ventured the opinion that most of the findings were due to the asphyxia that anaphylaxis induces in the guinea-pig. In 1911, Auer,[3] studying the heart of the rabbit during anaphylaxis by direct and graphic observation, reported the presence of heart block. In 1913, Auer and Robinson [4] undertook a thorough electrocardiographic investigation of the heart of the rabbit during anaphylaxis, and they concluded that disturbances in conduction ranging from slight delay to partial and complete heart block are rather constant in this condition, suggesting that anaphylaxis may play a rôle in cardiac disturbances in man.

The present study was undertaken to establish electrocardiographically the series of changes in the heart of the guinea-pig and in that of the rabbit during anaphylaxis, and to determine whether the changes are due to a direct and specific influence of the anaphylactic process on the myocardium. For this purpose, we shall indicate the results obtained by the electrocardiographic studies of the guinea-pig in acute asphyxia and in anaphylaxis, and those obtained in the rabbit in asphyxia and anaphylaxis and in a condition artificially simulating that of anaphylaxis, namely, the state following clamping of the pulmonary artery.

EXPERIMENTAL WORK

EXPERIMENT 1.—*A. Electrocardiographic Study Following Artificial Asphyxia in the Guinea-Pig.*—The following technic was used in the experiment.

For this study guinea-pigs weighing about 350 Gm. were used. In six animals the cardiac changes resulting from artificial asphyxia were demonstrated. The hair of both fore legs and the left hind leg was cut, and the legs were scrubbed well with soap and water and then with a hot saline solution. The guinea-pig was stretched on an animal board, and an electrocardiogram was taken with electrodes leading from the extremities. Following light ether anesthesia, the trachea was carefully exposed, and another tracing was taken. Asphyxia was subsequently induced by clamping the trachea. In two of the guinea-pigs tracings were made with indirect electrodes. In the remaining four, the chest was opened after the trachea had been clamped, and the nonpolarizable, direct electrodes of Noyen were employed. One electrode was placed in the region of the right

2. Königsfeld, H., and Oppenheimer, E.: Electrokardiographische Untersuchungen beim anaphylaktischen Shock des Meerschweinchens, Klin. Wchnschr. **1**:849 (April 22) 1922.

3. Auer, J.: Lethal Cardiac Anaphylaxis in the Rabbit, J. Exper. Med. **14**: 483, 1911.

4. Auer, J., and Robinson, G. Canby: An Electrocardiographic Study of the Anaphylactic Rabbit, J. Exper. Med. **18**:450, 1913.

auricle, the second in the region of the left auricle and the third touching the tip of the left ventricle. Tracings were thus taken with both indirect and direct electrodes, until cardiac standstill was observed.

The electrocardiographic tracings were practically the same for all animals, and therefore we shall tabulate the findings for only one. The tracings are from lead II and represent indirect leads unless otherwise indicated. The rate was 330 per minute, and was practically uninfluenced by ether anesthesia. Both auricles and ventricles were regular. The P-R interval was 0.05 second. The QRS complex was 0.03 second. The waves had the normal configuration and direction. T was postive in lead II (fig. 1 *A* and *B*). The trachea was clamped with a hemostat and thirty seconds later, just as symptoms of asphyxia were beginning to appear, the heart rate slowed to 300 per minute. The T

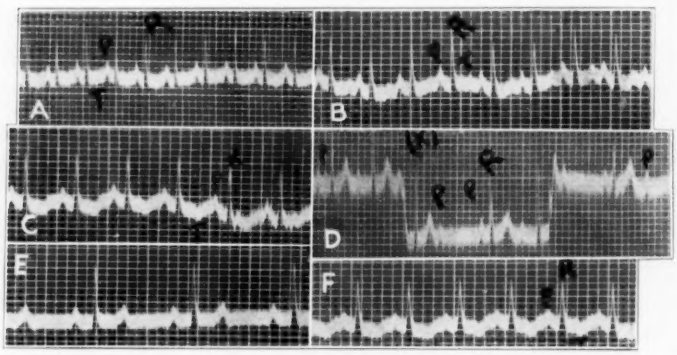

Fig. 1.—*A*, before anesthesia; the rate was 330; the P-R interval, 0.05 second. *B*, during anesthesia; the rate was 330. *C*, thirty seconds after the trachea had been clamped; the rate was 300; the P-R interval, 0.07 second; T, negative. *D*, transition from the normal mechanism (*x*); the auricular rate was 300; the ventricular rate, 150. *E*, 2:1 block; the auricular rate was 300; the ventricular rate, 150, three minutes later. *F*, the tracheal clamp had been released; the mechanism is normal.

wave became inverted in lead II and more pronouncedly so in lead III, and the P-R interval lengthened somewhat (0.07 second) (fig. 1 *C*). The next observed change is seen in figure 1 *D* and *E*; the ventricular rate was still slower, 150 per minute, while the auricular rate was 300 per minute, the ventricles responding only to every second auricular contraction. The P-R interval was 0.1 second. Lead III shows the same changes, except that P is shown superimposed on T. When the tracheal clamp was released four and a half minutes after it was applied (fig. 1 *F*), the normal mechanism was reestablished, only to give way

to 2:1 and later to 3:1 heart block on reapplication of the clamp (fig. 2 *A* and *B*). Complete dissociation of auricles and ventricles, and a high T take-off are seen in figure 2 *C*. The ventricular complexes bear no relation to the auricular representative. The presence of complete heart block is better seen in figures 2 *D* and 3 *A*. These show a general tendency to a lowering of the ventricular rate, with an increase in the QRS interval and a more marked abnormality of this complex, showing its origin to be lower in the ventricles. Thus, figure 2 *D*, using direct leads, shows the following: The auricular beat was 180 per minute, the ventricular rate, 60 per minute, and the QRS complex, 0.2 second and bizarre, appearing not unlike that of a block of the right

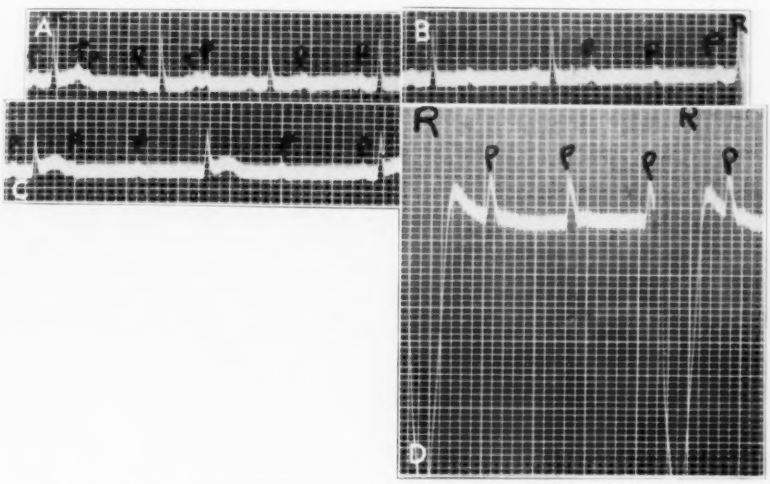

Fig. 2.—*A*, the trachea had been clamped again; there was a 2:1 block in one minute. *B*, partial 2:1 and 3:1 block, two minutes later; the auricular rate was 210; the ventricular rate, 90. *C*, there was complete heart block in four minutes; high T take-off. *D*, direct leads; there was complete heart block six minutes later; the auricular rate was 180; the ventricular rate, 60; the QRS complex, 0.2 second; there was a tendency toward a 3:1 block.

branch of the bundle. Subsequently the rate became much slower, so that in figure 3 *A* the auricular rate was 100 per minute, the ventricular rate, 20 per minute, and the QRS interval, 0.32 second. Somewhat later (fig. 3 *B*), the auricles ceased beating rhythmically, so that they showed fibrillation, while there was still evidence of idioventricular rhythm, with a further increase in the QRS interval to 0.48 second. This was followed by auricular standstill (fig. 3 *C*).

B. Electrocardiographic Studies in Anaphylaxis in the Guinea-Pig.—The following technic was used.

Guinea-pigs were passively sensitized to egg white by the intraperitoneal injection of 0.2 cc. of an antiegg rabbit serum of high titer (1:10,000). About twenty-four hours later anaphylactic shock was brought about by the intravenous injection of 0.3 cc. of 50 per cent whole egg white. Electrocardiographic tracings were taken before the injection of egg white and during the appearance of anaphylactic symptoms, with both indirect and direct leads.

There was apparently nothing of note about the normal curve obtained during anesthesia. The rate was 300 per minute. The P-R

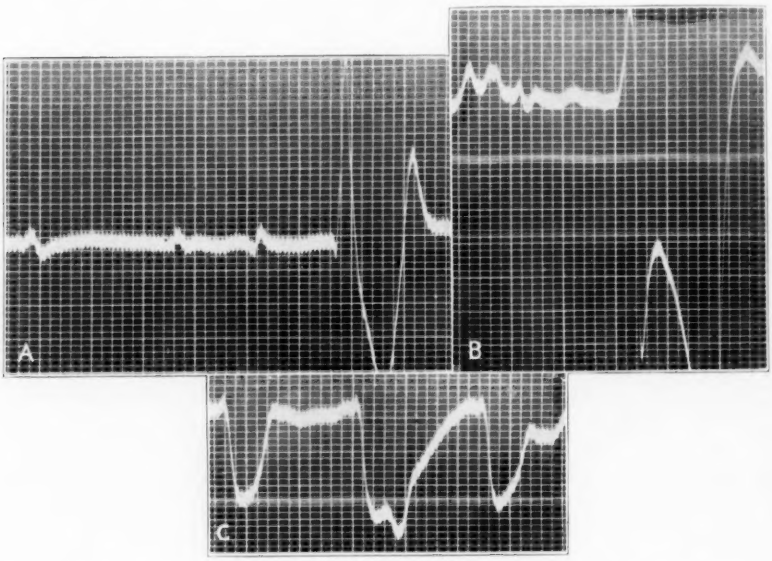

Fig. 3.—*A*, complete block; direct L; the auricular rate was 100; the ventricular rate, 20; the QRS complex, 0.32 second; there was an occasional auricular extrasystole. *B*, complete block; auricular fibrillation. *C*, ventricular fibrillation, followed by cardiac asystole.

interval was 0.04 second, and the QRS complex, 0.03 second. Arrhythmia was not evident (fig. 4 *A*). Following the injection of egg white and the subsequent development of anaphylactic symptoms, certain progressive changes occurred. Thus, as figure 4 *B* shows, the rate was slowed, with the subsequent establishment of 2:1 block, so that, while the auricular rate was 180 per minute, the ventricular rate was 90 per minute. This condition of "dropped beats" alternated with normal beats, during which the P-R interval was increased to 0.1 second. The

T wave became inverted (fig. 4 *C*), the general tendency being toward 2:1 block with the rate still slower; the ventricular rate was about 75. The ventricles slowed down further, so that they beat about 30 per minute and independent of the auricles, a tendency toward 2:1 and 4:1 block. The T wave was negative in all leads; it took off below the line, and the R-T interval was short. Complete dissociation of rhythm

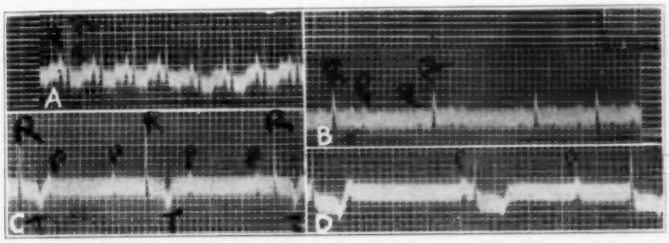

Fig. 4.—*A*, normal; rate, 300. *B*, anaphylaxis in one minute; 2:1 block; the auricular rate was 180; the ventricular rate, 90. *C*, inverted T, two minutes later; the ventricular rate was 75. *D*, complete block, three minutes later; the auricular rate was 90; the ventricular rate, 40.

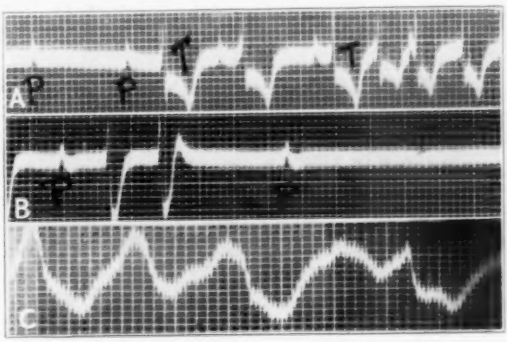

Fig. 5.—*A*, complete block, three minutes later; paroxysmal ventricular tachycardia, 240; the auricular rate was 120; T, negative, with a low T take-off. *B*, the auricular rate was 60; there were long periods of ventricular asystole. *C*, ventricular fibrillation.

followed (fig. 4 *D*). This condition became more marked, with evidence of branch bundle block (the QRS complex was 0.4 second), until, fourteen minutes from the development of the initial symptoms of anaphylactic shock, the auricles beat regularly while there were a series of ectopic ventricular beats and complete dissociation of rhythm. Ventricular fibrillation finally preceded cardiac standstill (fig. 5).

EXPERIMENT 2.—*A. Electrocardiographic Study Following Clamping of the Pulmonary Artery of a Rabbit.*—The following technic was used in the experiment.

Electrocardiographic tracings were taken before and during light ether anesthesia in normal rabbits. The two fore legs and the left hind leg were cleaned of hair and scrubbed with a hot saline solution. Tracings were thus taken with indirect leads. The chest was opened, and artificial respiration was employed. An attempt was made to duplicate the condition of obstruction in the pulmonary circuit seen in anaphylaxis by clamping off the pulmonary artery. Tracings were again taken with direct leads, the nonpolarizable electrodes of Noyen being used; the electrodes were placed over the right auricle, the left auricle and the tip of the left ventricle.

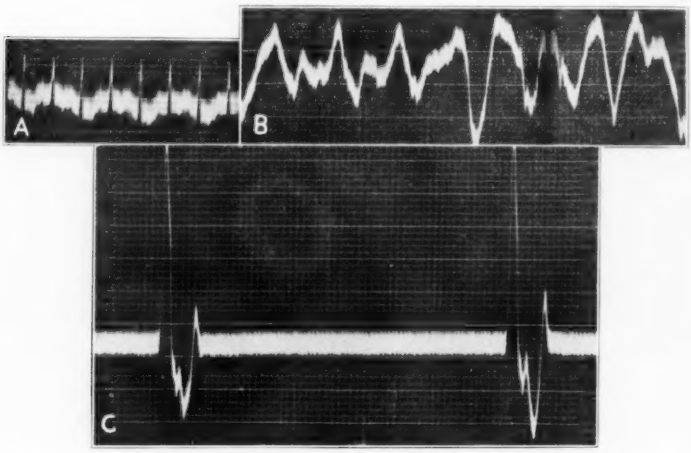

Fig. 6.—*A*, normal. *B*, the pulmonary artery was clamped; there was ventricular fibrillation. *C*, auricular standstill; the QRS complex was 0.28 second.

The normal tracing showed nothing of note. Continuous tracings were taken. Almost immediately following clamping of the pulmonary artery, the ventricles began to fibrillate (fig. 6 *B*). Space does not permit the inclusion of longer strips of these tracings, but they show various degrees of disturbed cardiac mechanism ending in auricular and ventricular fibrillation. The sequence of these various disturbances in mechanism was not always the same. This apparently was due to the time interval between tracings, or to the condition of the muscle of the heart. The foregoing analysis does show, however, that clamping the pulmonary artery produces relatively sudden and profound changes in the cardiac mechanism in the rabbit.

B. Electrocardiographic Studies Following Artificial Asphyxia in the Rabbit.—Artificial asphyxia was produced in several rabbits by clamping the trachea. Tracings were taken with indirect and direct leads as described.

There were no appreciable changes before or during ether anesthesia. The rate was 360 and regular. The P-R interval was 0.06 second; the QRS complex, 0.03 second. T was positive in lead II (fig. 7 *A*). When the trachea was clamped (fig. 7 *B*), there was a definite slowing of ventricular rate to 120 per minute, and a tendency toward nodal rhythm. However, two minutes later, and apparently without any explainable cause, normal mechanism was established (fig. 7 *C*), with right ventricular predominance and a definite increase in the P-R interval to 0.1 second. T was still positive in leads I and II. Shortly afterward (fig. 8 *A*), there was a further increase in the P-R interval to 0.12

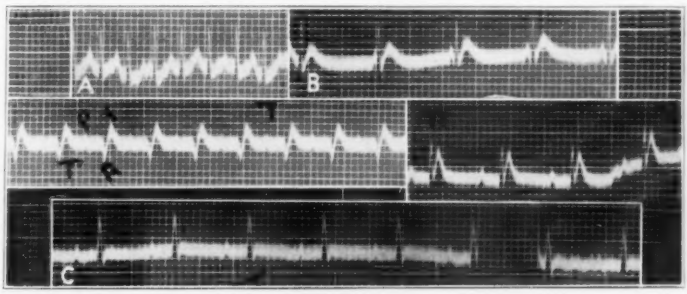

Fig. 7.—*A*, normal tracing; rate, 360; P-R interval, 0.06 second; QRS complex, 0.03 second. *B*, the trachea had been clamped; there was nodal rhythm; rate, 120; T, positive. *C*, three leads; normal mechanism (two minutes); P-R interval, 0.12 second; there was a right ventricular predominance.

second, with a sudden change in the character of the QRS complex; two minutes later nodal rhythm was reestablished, only to give way (fig. 8 *C*) to an antemortem type of fibrillation and cardiac standstill.

C. Electrocardiographic Study of Anaphylaxis in the Rabbit.—The following technic was used.

In order to study the effect of anaphylactic shock on the heart of the rabbit, several rabbits were actively sensitized with egg white, the technic suggested by Coca and Grove being employed: "A primary intravenous injection is made of 0.5 cc. of 50 per cent egg white (first day); on the sixth day 5.0 cc. of whole egg white are injected intraperitoneally; on the eleventh day and on the succeeding seven days 1.0 cc. of whole egg white is injected intraperitoneally. The animals are allowed to rest one week and then receive 4 or 5 cc. of undiluted whole egg white subcutaneously. On the sixth day thereafter serum is obtained from each animal and the precipitating titer is determined by layering dilutions of whole egg

white over the undiluted serum in the conical ring test tubes. Rabbits whose serum shows a titer of over 1 to 5000 or more as a rule are good subjects for anaphylactic shock." This was induced by the intravenous administration of 5 cc. of 50 per cent egg white. Tracings were taken before and during shock immediately after the onset of the initial symptoms of anaphylactic shock.

Auricular fibrillation was seen (fig. 9 *B*). T_2 became negative, and only a few seconds later, 2:1 heart block appeared (fig. 9 *C*). Thirty

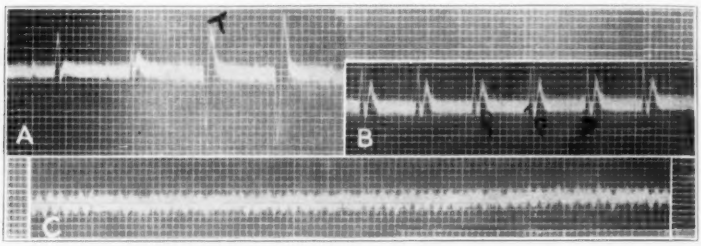

Fig. 8.—*A*, continuous with figure 1 *C*; delayed conduction. *B*, rate, 120; nodal rhythm, two minutes later. *C*, ventricular fibrillation.

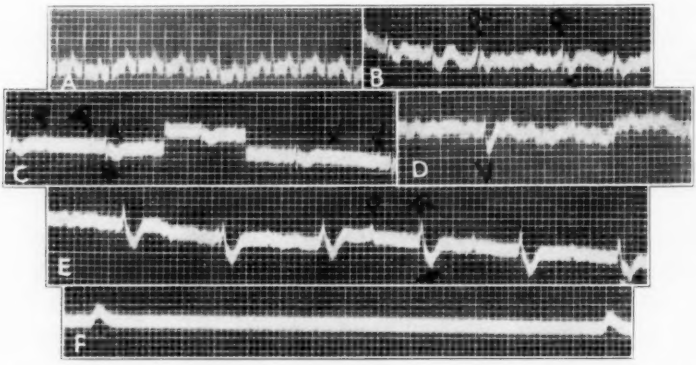

Fig. 9.—*A*, normal; rate, 360; P-R interval, 0.06 second. *B*, anaphylaxis; auricular fibrillation; rate, 180; T_2, negative. *C*, continuous with figure 1 *B*; rate, 110; 2:1 block. *D*, auricular fibrillation; ventricular rate only 15. *E*, delayed conduction; rate, 110; QRS complex, 0.06 second; T, negative; P-R interval, 0.24 second. *F*, auricular standstill for five minutes; ventricular rate, 15, irregular.

seconds later, the auricles were still fibrillating (fig. 9 *D*), but the ventricular rate was only 15 per minute. This condition changed to that seen in figure 9 *E*, which shows the ventricular rate to be 110. The P-R interval was 0.24 second, or almost four times longer than normal. T was inverted in lead II. Complete block followed, and,

finally, five minutes later (fig. 9 *F*), there was complete auricular standstill accompanied by a slowly and irregularly beating ventricle at the rate of about 15 per minute.

PATHOLOGIC SECTIONS OF THE HEART AND LUNGS IN GUINEA-PIGS AND RABBITS

Examination of sections of the heart during anaphylaxis did not show definite pathologic changes. Dr. Mortimer Cohen, of the department of pathology of the University of Pittsburgh, furnished sections of the heart and the lungs of guinea-pigs and rabbits that died during anaphylaxis for study. Sections of the heart showed nothing of note. Sections of the lungs of guinea-pigs showed definite constriction of the bronchi and bronchioles with some degree of emphysema. Those of the lungs of rabbits showed a marked constriction of the pulmonary arterioles.

COMMENT

From an analysis of the electrocardiograms obtained from the artificially asphyxiated guinea-pig and from the guinea-pig during anaphylaxis, it appears that the profound changes in cardiac mechanism are analogous in the two conditions. One notes in both a similar and definite train of events: (1) slowing of the rate with normal mechanism; (2) the appearance of partial heart block, followed by total block, branch bundle block, occasional nodal rhythm, auricular fibrillation, ventricular fibrillation and paroxysmal ventricular tachycardia, and (3) either auricular or ventricular asystole, followed by cardiac standstill. It is interesting to point out that practically all of the tracings taken during asphyxia and anaphylaxis showed an inversion of the T wave in lead II, with a shortened R-T interval and the T wave starting either above or below the line. In the rabbit, the cardiac changes following acute asphyxia, anaphylaxis or clamping of the pulmonary artery are essentially the same; that is, the picture is that of profound myocardial involvement accompanied by disturbed rhythm, leading finally to cardiac death. It appears, therefore, that the disturbances in the cardiac mechanism are more or less similar during anaphylaxis in both the guinea-pig and the rabbit, in spite of the fact that the pathologic physiology of anaphylaxis differs in the two species. Although death in the guinea-pig is due to a constriction of the bronchi and bronchioles with inability to expire the air from the lungs, while in the rabbit it is due to constriction of the pulmonary arteries and arterioles with damming back of blood into the right side of the heart and circulatory failure, this difference in the mode in which anaphylaxis proves fatal in the two species bears no influence on the resulting cardiac disturbances as revealed by the electrocardiogram. The cardiac changes

in both animals must be due primarily to interference with the blood supply to the heart, that is, myocardial anoxemia, although cerebral anoxemia is, no doubt, also a factor. This is shown to be true by the fact that with restoration of ventilation normal mechanism is reestablished (fig. 1 *F*). The abnormal mechanism described is therefore due to the factors presented and not to the specific effect of anaphylaxis as thought and described by Auer.[5]

The myocardium and the conducting mechanism are affected not only by the state of anoxemia referred to, but also by the irritating effect of lactic acid and the various katabolites that have been demonstrated to exist in asphyxia.[6] Thus disturbances in rhythm occur long before there is any mechanical interference with the circulation.[7]

The exact rôle played by the vagus nerve in producing the cardiac changes discussed in this paper is not clear. While it has been demonstrated experimentally that stimulation of the vagus nerve may produce various forms of arrhythmia, the impression of various workers, notably Roaf and Sherrington,[8] Sherrington,[9] Matheson [10] and Lewis and Matheson,[11] seems to be that the influence of the vagus nerve is not very important, for its removal by atropine or section does not interfere with the occurrence of heart block.[4] Furthermore, similar results are obtained in the spinal animal in which the cardioinhibitory center is absent.

SUMMARY

1. Electrocardiographic changes in the guinea-pig are analogous in artificial asphyxia and anaphylaxis.

2. The changes consist of bradycardia, partial and complete block, inversion of the T wave, with a shortened R-T interval and a high T take-off, and auricular and ventricular fibrillation.

3. The changes in the T wave are not unlike those noted in coronary occlusion and suggest the possibility that disturbances in the cardiac mechanism may be due to myocardial anoxemia.

5. Auer, J.: Ueber den plötzlichen anaphylactischen Tod beim Kaninchen, Zentralbl. f. Physiol. **24**:957 (Jan. 7) 1910.

6. Kaya and Starling: J. Physiol. **39**:346, 1909. Sherrington: J. Physiol. **38**:381, 1909. Fletcher and Hopkins: J. Physiol. **35**:247, 1906-1907.

7. Robinson, G. Canby: Am. J. Physiol. **31**:18, 1912-1913.

8. Roaf and Sherrington: Quart. J. Exper. Physiol. **3**:209, 1910.

9. Sherrington: J. Physiol. **38**:375, 1909.

10. Matheson, G. C.: The Cause of Heart Block Occurring During Asphyxia, Heart **2**:55, 1910-1911.

11. Lewis, Thomas; and Matheson, G. C.: A-V Heart Block as a Result of Asphyxia, Heart **3**:47, 1910-1911.

4. The foregoing conclusions are also true of the rabbit during asphyxia, during anaphylaxis and in a condition following clamping of the pulmonary artery.

5. Microscopic sections of the hearts of guinea-pigs and rabbits revealed nothing of note as a physical basis for the changes observed.

6. The vagus nerve does not seem to play an important rôle in the production of the disturbances in mechanism.

7. The functional cardiac changes observed in the guinea-pig and rabbit during anaphylaxis are not specifically due to the anaphylactic state, but rather to the state of asphyxia that anaphylaxis induces.

Dr. C. C. Guthrie gave helpful suggestions, and Mr. J. Lawler gave technical assistance in the preparation of some of the material for this paper.

1004 May Building.

SUBACUTE MENINGOCOCCAL ENDOCARDITIS*

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Imitating Libman, who prefers the term subacute streptococcal endocarditis to that of subacute bacterial endocarditis when speaking of the more chronic *viridans* type of infection, I have ventured to make use of the title presented, in connection with a case of infective endocarditis of long duration. This I do the more readily, first, because the classic picture of subacute bacterial endocarditis was so faithfully reproduced over a course of many months; secondly, because the meningococci were the only organisms isolated in culture from the blood and spinal exudate, and, finally, because I had the further good fortune in the consideration of this case to be able to submit the history and specimens to Dr. Libman who, being more familiar with the occasional case of subacute bacterial endocarditis due to organisms other than *Streptococcus viridans,* was able to give me much necessary and useful information about these less common forms of infection.

There are doubtless many objections to be urged against the employment of a new term, and it is realized that the familiar picture of subacute bacterial endocarditis has become something which in one's mind is usually associated with infection by *S. viridans;* yet it is to be remembered that *Bacillus influenzae, Staphylococcus aureus* and the gonococcus, are credited with the production of a certain small percentage of those cases labelled subacute bacterial endocarditis and running a more or less typical course, so that it is therefore probable that other organisms will be found capable of giving rise to the same set of symptoms and physical signs.[1]

That this is a possible viewpoint seems to be indicated by the article of de la Chappelle,[2] who reported a case presenting all the features of

* Submitted for publication, March 23, 1931.

* From the service of Dr. Duncan Graham, Toronto General Hospital, and reported with his permission at the Section of Medicine of the Toronto Academy of Medicine.

1. Horder, T. J.: Bacillus Influenzae as a Cause of Endocarditis, Tr. Path. Soc. London **57**:58, 1906. Libman and Cellar: Observations on the Etiology of Sub-Acute Infective Endocarditis, Tr. A. Am. Physicians **25**:5, 1910. Smith, F. J.: The Influenza Bacillus as a Cause of Fatal Endocarditis After Eight Years (?), Lancet **1**:1201, 1908. Simons, I.: Critical Review: Bacterial Endocarditis, Quart. J. Med. **7**:291, 1913-1914. Libman: M. Clin. North America **2**:117, 1918. Marmorstein, M.: Contribution à l'étude des aortites grippales, Rev. de méd. **28**:267, 1918.

2. de la Chappelle: Am. Heart J. **4**:732 (Aug.) 1929.

subacute bacterial endocarditis, yet yielding only *Brucella abortus* in cultures before and after death; he referred also to other cases [3] of endocarditis associated with *Brucella* infection, cases which, in one instance at least, were suggestive to a degree, with their early history of rheumatic fever and mitral disease and their subsequent course, of long drawn out infection with multiple embolic accidents. It is quite evident that the authors reporting some of these early cases hesitate to imply that *Brucella abortus* can behave like *S. viridans* in causing a chronic endocarditis resembling the subacute bacterial form; de la Chappelle, however, does not seem to be so conservative in his ideas, and on reading his contribution one is tempted again to suggest that the old rheumatic valve lesion may freely invite invaders other than *S. viridans* and *B. influenzae*, invaders that may adapt themselves to the more chronic form of warfare, represented by a prolonged course, embolic accidents, enlargement of the spleen, clubbed fingers, pigmentation of the skin and an abundant growth of vegetation on the valves. Whether or not one will find that these invaders provoke quite the same response in the tissues as do the streptococci of the *viridans* type cannot yet be stated. Such lesions as the Bracht-Waechter bodies in the heart muscles and the peculiar reaction in the kidneys may well be something not produced by every form of irritant or infection, and the question may be raised whether in these less common types of cases a previous *viridans* infection may not have died out, allowing other organisms to be found as late saprophytic invaders of the blood stream. This would seem unlikely and, in a few instances at least, immunologic reactions in the serum have pointed clearly in the other direction. Three distinct diseases, a chronic rheumatic and a subacute *viridans*, followed by a third, an acute meningococcus infection (as in the case to be reported), and all localized on the same heart valve would seem an anomalous condition indeed.

Endocarditis of an acute form has long been recognized as a complication of meningococcus meningitis. The reports of Cecil and Soper,[4] and Warfield and Walker [5] are interesting in that they were the first to detail acute meningococcus endocarditis occurring in the absence of meningitis "meningococcal septicemia with involvement of the heart valves." These cases have been more properly considered as acute bacterial endocarditis, running a course as they did of twenty-four days and six weeks,

3. Scott: Am. J. M. Sc. **175**:66, 1928. Evans, A. C.: Hygienic Laboratory Bulletin, 1925, p. 143. Marlow, F. W.: Meningococcemia, J. A. M. A. **92**:619 (Feb. 23) 1929.

4. Cecil, R. L., and Soper, W. B.: Meningococcus Endocarditis, with Septicemia, Arch. Int. Med. **8**:1 (July) 1911.

5. Warfield and Walker: Bull. Ayer Clin. Lab., Pennsylvania Hospital, 1903, no. 1, p. 81.

respectively; the same could be said of the case reported by Drought and Kennedy [6] and of most of the recorded instances of meningococcus endocarditis. Wright and Mackerwell,[7] however, described an endocarditis of sixteen weeks' duration in which they found meningococci in the vegetations on the mitral valve; this case might well be called, in point of time at least, subacute bacterial endocarditis; while MacMahon and Burkhardt [8] stated that in their case of meningococcus endocarditis the appearance of the patient was such that the diagnosis of subacute bacterial endocarditis was suggested, although the course of the infection and the Janeway spots were more in keeping with the acute form of the disease. In Morgan's [9] two patients with meningococcal septicemia, both of whom recovered after an illness of three and four months, the history and physical findings were strangely suggestive of the subacute form of bacterial infection of the heart valves, with the observations on the blood, the prolonged fever and the crops of nodes. It is possible, as Herrick [10] suggested, that many of the curious examples of chronic meningococcal blood stream infections which have gone on to cure have been subacute or chronic cases of meningococcus endocarditis which have become spontaneously bacteria-free; in general, however, the picture of a subacute bacterial endocarditis has not often been simulated by a meningococcal infection, and the history here given may therefore be of interest.

REPORT OF A CASE

Mrs. H., aged 37, had been attending the outpatient department for eight months, complaining of headache and pain in the chest. The diagnosis of subacute bacterial endocarditis had been made as a result of finding fever, a large heart, a loud systolic murmur in the mitral area and a diastolic murmur in the aortic area, together with the facts that the spleen and liver were both enlarged, that the fingers were clubbed and that the skin had the café-au-lait color so often spoken of as being present in this disease. It had also been noted that from time to time small petechiae had appeared in the skin and that there had been present albuminuria with casts and red blood cells on microscopic examination. The patient had been under constant observation and on three occasions had been found unconscious. There had been no determination, however, of the cause of the unconsciousness.[11] A few days before her admission to the hospital, headache had become quite severe and signs of meningitis developed; she complained of pain in her joints and it was noted that again there was a crop of petechiae. There were at this time several tender spots on her fingers which suggested Osler

6. Drought and Kennedy: Cerebral Spinal Fever, London, A. & C. Black, 1919.

7. Wright and Mackerwell: J. Roy. Army M. Corps **25**:353, 1915.

8. MacMahon and Burkhardt: Am. J. Path. **5**:197 (May) 1929.

9. Morgan: Bull. Johns Hopkins Hosp. **32**:245 (Aug.) 1921.

10. Herrick, W. W.: Extrameningeal Meningococcus Infections, Arch. Int. Med. **23**:409 (April) 1919.

11. Cerebral embolism was suspected.

nodes. She was in the ward for two weeks, during which time two blood cultures were positive for meningococci and lumbar puncture brought away cloudy fluid from which meningococci were cultivated on four different occasions. It was interesting to note that in spite of the general infection the white blood count remained low, ranging between 6,000 and 12,000. The petechial eruption was profuse, albumin was present in large amounts and, as in previous examinations, there were numerous casts and blood cells in the urine. There was increased intracerebral pressure as was indicated by the distinct edema of the optic disks; she remained, however, clear up to within two days of her death, and presented at all times a picture more in keeping with the *viridans* subacute form of bacterial endocarditis, so that I was surprised to a degree to find that I was dealing with an infection due to the meningococcus. Whether this was the organism that had initiated the illness eight months previously might, according to the arguments already made use of, be a matter for debate. Dr. Libman, however, seemed willing to accept the evidence as presented, and certainly the course of the disease and the postmortem findings conform to what one had been used to consider as making up the picture of subacute bacterial endocarditis.

Autopsy,[12] performed a few hours after death, demonstrated that there was, as expected, a diffuse meningo-encephalitis affecting the brain and spinal cord. From the exudate, produced by the inflammation, meningococci were easily cultivated. The spleen was large, weighed 360 Gm. and showed several infarcts. The liver was enlarged and both kidneys were large; both kidneys showed a pale red cortex; the glomeruli were prominent and there were fresh and old infarcts in both organs; the right kidney weighed 170 Gm.; the left, 195 Gm. There was nothing striking in the other organs save the evidence of a terminal lobular pneumonia in both lungs.

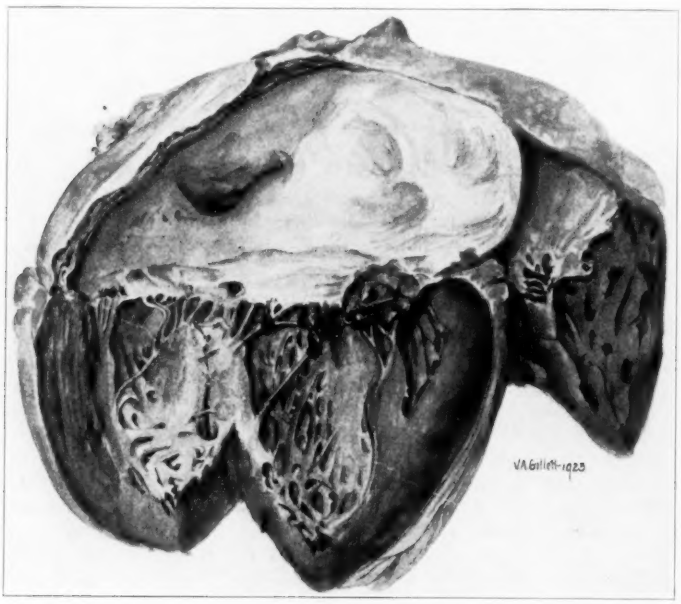
The heart, of course, was the organ in which I was most interested and I was fortunate in getting a water color reproduction at the time of the autopsy (see figure). The picture reproduced therefrom shows the moderate degree of enlargement of the left ventricle and the dilated left auricle, together with the thickening of the mitral valve and the shortening and retraction of the chordae tendineae, so indicative of an earlier rheumatic infection. At one point of the mitral valve marked destructive ulceration is present, and the granulations characteristic of the endocarditis are well depicted. The aortic valve was clear. Nothing grew in cultures from the vegetations on the valves.

Sections were made of the mitral valve and of the heart muscle and were reported on as follows: "The section shows about 1 cm. of the valve curtain including its free edge. There is a marked nodular thickening present which involves the distal 8 mm. of the cusp and rises abruptly to a maximum height of 6 mm. from the outer surface. The apex of this nodule bears a crater-like area of ulceration measuring 4 mm. at its mouth and 3 mm. in depth. The disrupted surface is overlaid with a ragged incrustation of thrombotic material rich in polymorphonuclear leucocytes and containing many blue staining clumps of bacteria, the morphology of which could not be accurately made out. The vegetation is composed largely of fibrous tissue. At the base this tissue is of the mature variety rich in collagen and having scanty slit-like nuclei, while around the ulcerated area the growth is more cellular and resembles granulation tissue. Between these two extremes is a wide area of oedematous connective tissue which contains many blood vessels engorged with erythrocytes. The inflammatory

12. Pathologic and bacteriologic records are from the service of Professor Klotz.

reaction present in and around the ulcerated area has infiltrated widely the interstices of the surrounding fibrous tissue. Deep to the area of ulceration interrupted masses of polymorphonuclear neutrophiles extend right through to the septal surface of the cusp where the endothelium is disrupted for a short distance. There is unmistakable evidence here of healed lesions which preceded the angry looking acute ulcerative process now present.

"Section of the myocardium shows the presence of an acute inflammation characterized by the presence of a few polymorphonuclear cells between the muscle bundles, and oedema of the interstitial tissue. There is also some scarring along the vascular channels indicative of a chronic myocarditis. This moderate perivascular sclerosis is diffuse and in many instances is nodular. The picture is very



Subacute meningococcus endocarditis.

suggestive of rheumatic infection but no Aschoff bodies can be seen. Professor Klotz was of the opinion that the old condition was probably rheumatic though unable to make a positive diagnosis."[13]

As stated, both kidneys were large and pale, with a reddened cortex. The glomeruli were prominent and there were many small infarcts in evidence. The kidney sections seemed to show that an acute nephrosis had been engrafted on an acute interstitial and acute diffuse glomerulonephritis. The report as received from the Pathological Department of the Toronto General Hospital reads as follows: "Many acute foci of inflammation were present in the inter-

13. The report on the valve sections and heart muscle was made by Dr. Klotz and Dr. T. H. Belt.

stitial tissue and there was a diffuse involvement of the glomeruli. In addition a well marked degenerative process was present in the tubular epithelium. The whole picture evidenced an acute lesion, there being no fibrous change. The focal inflammatory lesions were perivascular, located in close relationship to both large and small vessels. There were more and larger infiltrations in the subcortical regions, where the arterial supply divides, than in either cortex or medulla. The polymorphonuclear leucocyte was the chief cell taking part in the reaction. The focal lesions were confined almost entirely to the interstitial tissue but occasionally they invaded tubules giving rise to small cellular casts within the denuded lumina. Not infrequently the inflammation was seen in intimate relationship to the afferent arterioles of the glomeruli and in such instances the adjacent group of tubules were often completely hyalinized and necrotic. The glomeruli were large and uniform in appearance. The capsular spaces were dilated but, for the most part, free from wandering cells. The glomerular tufts were swollen and presented a striking cellular increase; not only did they contain a number of leucocytes but the clothing endothelium had undergone a proliferative change. The loops were devoid of blood. Bowman's capsules were not thickened but occasionally showed some exfoliation. There was no fibrous proliferation anywhere to indicate a subacute or chronic process. Diagnosis: (1) acute diffuse glomerulonephritis; (2) acute interstitial nephritis (focal); (3) acute nephrosis."

In a personal communication, Dr. W. L. Robinson said that this kidney picture is not incompatible with the diagnosis of subacute bacterial endocarditis.

COMMENT

In the foregoing report, there is little deviation from the classic picture of subacute bacterial endocarditis. We have suggested that the possibility of an earlier *viridans* infection of the valves be considered in the final summing up, an infection which may have died down only to be supplanted by one due to the meningococcus. It must be remembered, however, that the history given was one of a continuous febrile illness of eight months' duration. A determination as to the time at which one infection might have ceased and another begun is therefore impossible. If two distinct infections had been in existence, one must reckon with the fact that at no time did they produce a different set of symptoms. Meningitis may be the terminal accident in a case of chronic *viridans* endocarditis, as has been pointed out by Smith and Brumfield.[14] In the case reported by these writers, the meningitis was apparently due to an infection by *S. viridans*. In the present case, I had the feeling that *S. viridans* would be found as the infecting agent in the meningitis which finally developed. One point of interest must be touched on. From the beginning to the end of this patient's illness, there was a constant appearance of the Osler nodes rather than the Janeway spots. This must always be held to suggest the subacute and chronic infection as opposed to the more acute type.

14. Smith and Brumfield: Am. Heart J. **2**:446 (April) 1927.

It is now recognized that infection by the meningococci may assume a very chronic form; the possibility that those chronic septicemias may mean that the meningococci have lodged on a heart valve must always be thought of. Many of these chronic meningococcal septicemias have gone on to cure without showing signs of involvement of either brain or endocardium, and after months of positive blood cultures. The disappearance of organisms from the blood stream may indicate the spontaneous cure of an endocarditis, such as is occasionally recorded in cases of subacute bacterial endocarditis due to *viridans* infection. Such recoveries seem to occur with considerable frequency in the course of these meningococcal septicemias, and it would appear that if the brain and spinal cord are not attacked, recovery may follow even without antimeningococcus serum.

It is not necessary at this moment to discuss these chronic meningococcal septicemias. A large literature is growing up on the subject. Among many articles to be referred to are those by Bloedorn,[15] Weichselbaum and Ghon,[16] Rhoads,[17] Bray,[18] Montgomery,[19] Bourdelles,[20] Dock,[21] Finlay and Rhea,[22] Hay and Huyck,[23] Andrewes,[24] Cabot [25] and Vesell and Barsky.[26] Herrick's suggestion that these chronic septicemias may represent an endocarditis has been referred to. The description of Morgan's cases leads one inevitably to suggest that an endocarditis was present. His descriptions are those of cases of subacute bacterial endocarditis as one is used to seeing them. It is possible that in the present case, recovery might have ensued if the brain and spinal cord had not been attacked.[27]

15. Bloedorn: Am. J. M. Sc. **162**:881, 1921.

16. Weichselbaum and Ghon: Wien. klin. Wchnschr., 1905, p. 24.

17. Rhoads: Am. J. Path. **3**:623, 1927.

18. Bray, H. A.: Chronic Meningococcus Septicemia Associated with Pulmonary Tuberculosis, Arch. Int. Med. **16**:487 (Sept.) 1915.

19. Montgomery: Canad. M. A. J. **20**:266 (March) 1929.

20. Bourdelles: Presse méd. **36**:660, 1925.

21. Dock, W.: Intermittent Fever of Seven Months' Duration Due to Meningococcemia, J. A. M. A. **83**:31 (July 5) 1924.

22. Finlay and Rhea: Tr. A. Am. Physicians, 1912, p. 381.

23. Hay and Huyck: Canad. M. A. J. **19**:695 (Dec.) 1928.

24. Andrewes, F. W.: Lancet **1**:1172 (April 28) 1906.

25. Cabot, Richard: New England J. Med. **201**:139 (July 18) 1929.

26. Vesell and Barsky: Am. J. M. Sc. **179**:589 (May) 1930.

27. Since the writing of this article, there has appeared the report by Master, of New York, on "Meningococcemia with Endocarditis" (J. A. M. A. **96**:164 [Jan. 17] 1931). Three cases were reported in which the prolonged temperature, embolic accidents and cardiac signs suggested endocarditis. In all three cases meningococci were cultivated from the blood, antimeningococcus serum was used and recovery took place.

SUMMARY

1. A case is reported that for eight months showed symptoms and physical signs which one is accustomed to associate with infection of the heart valves by *Streptococcus viridans*—subacute bacterial endocarditis.

2. Blood cultures in the last two weeks of the illness were positive for meningococci.

3. Death took place as a result of invasion of the brain and spinal cord by the meningococci.

4. The observations at autopsy agree closely with those described as occurring in association with subacute bacterial endocarditis. Meningococci were recovered at autopsy from the meninges only. The lesions in the heart and kidney as described were apparently in accordance with those observations recorded at autopsy in cases of subacute bacterial endocarditis.

EFFECTS OF EXERCISE ON EXPERIMENTAL CARDIAC INFARCTION *

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Although extensive experimental studies have been made of the effects of ligation of the coronary arteries, apparently no review of the effects of exercise following experimental cardiac infarction has been made.

Knowledge of the effects of exercise at varying intervals after ligation should give information that could be transferred to the treatment of human beings. Accordingly a series of experimentally produced infarcts in dogs was studied as to the effects of regulated exercise.

Kolster [1] observed dogs living seventeen months after ligation of the ramus descendens anterior. Miller and Matthews [2] kept dogs alive for ninety days after ligation of the left coronary artery. Both described infarcts, and Miller and Matthews [2] observed marked thinning of the ventricular musculature near the apex.

Smith [3] observed the electrocardiographic changes following ligation of the ramus descendens anterior in dogs living up to sixty-three days. He is the first author to mention the effects of exercise, but gives no accurate data as to the amount or duration of the exercise.

In clinical literature reference is frequently made to the coincidence of hypertrophy in the presence of an occlusion of the coronary artery or of cardiac infarction. Experimentally, Stewart [4] observed cardiac hypertrophy after producing injury of the heart muscle by the injection of epinephrine hydrochloride. MacCallum [5] stated that sufficient experimental evidence is lacking on this point because of many other factors involved that may also cause hypertrophy. Eyster [6] believed that "the

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* From the Department of Physiology and Pharmacology, Northwestern University Medical School.

1. Kolster: Skandinav. Arch. f. Physiol. **4**:1, 1893: cited by Porter.

2. Miller, J. L., and Matthews, S. A.: Effect on the Heart of Experimental Obstruction of the Left Coronary Artery, Arch. Int. Med. **3**:476 (June) 1909.

3. Smith, F. M.: Ligation of Coronary Arteries, Arch. Int. Med. **22**:8 (July) 1918.

4. Stewart, H. J.: J. Clin. Investigation **3**:475, 1927.

5. MacCallum, W. G.: Textbook of Pathology, ed. 4, Philadelphia, W. B. Saunders Company.

6. Eyster, J. A. E.: Tr. A. Am. Physicians **42**:13, 1927.

question of physiological hypertrophy from simple cardiac stimulation or increased cardiac work due to muscular exercise is still an open one," and added that much of the experimental work is contradictory. It has been shown recently by Herrmann and Musser [7] that after the production of experimental pericarditis with adhesions, some hypertrophy always resulted. If these adhesions were relieved by a second operation, little hypertrophy occurred.

METHODS

In this study five dogs were used, each of which was trained to run on a motor-driven treadmill at a constant speed of a little over 3 miles an hour at an incline of 15 degrees. The training period extended over at least five days, and the time of each run was gradually increased until the dog was able to run for from thirty to sixty minutes with little or no signs of fatigue. Throughout this work a protocol of each run was recorded. These dogs were prepared according to the method described by Sutton and King.[8]

The operation was done aseptically, ether anesthesia and artificial respiration being used. An incision was made in the third left intercostal space, and the fibers of the pectoralis major muscle were separated with minimum injury. The pericardium was incised, and the ramus descendens anterior was ligated, usually from 1 to 2 cm. from its origin. X-ray photographs were taken before and again immediately after the operation. The x-ray technic and that of measuring the films was the same as that followed by Eyster.[6] Exposures of less than a second were taken at the end of inspiration, with a distance of 1 meter from the target to the film. The diastolic size of the heart as recorded on the x-ray plates was measured with the planimeter.

Exercise was started on the treadmill from two to six days after the ligation. The frequency of the exercise and the amount were increased in each succeeding dog as it was learned how much work the animal could endure. Any cardiac changes were followed by x-ray photographs, and the animals were weighed at frequent intervals.

RESULTS

After ligation in dog 2 (table 1), a six day rest period was allowed before exercise was started. The first run was for fifty minutes, and no signs of fatigue appeared. Thereafter exercise was given for from fifty to sixty minutes every fourth day for forty-four days. This animal was killed and an autopsy performed on it on the seventieth postoperative day. There were fibrous adhesions over the anterior surface of the left ventricle, and all that remained of the infarcted area was a small puckered area of fibrosis at the apex. The wall at this point was not thinner than normal.

Three animals were given exercise on the third postoperative day. The first (dog 4, table 2) had run ten minutes on the first day of exercise when fatigue and weakness made further exercise impossible.

7. Herrmann, G., and Musser, J. H.: Am. Heart J. **4**:268, 1929.

8. Sutton, D. C., and King, W. W.: Proc. Soc. Exper. Biol. & Med. **25**:842, 1928.

As the days passed, more and more exercise was possible, so that within nine days this dog could run for sixty minutes with relatively little fatigue. The exercise period was fixed at one hour, and experiments were conducted every second or third day for three weeks, during which time no discomfort was noticed. On the ninety-eighth day this dog was

TABLE 1.—*Dog 2*

Time of Examination	Diastolic Area of Heart in X-Ray Plate, Sq. Cm.	Pulse Rate	Running Period, Min.	Fatigue	Weight, Kg.	Comment
Before operation	73.3	96	50	+	16.0	
After operation	63.0	...	..	..	....	
22 days	69.1	72	50	+	13.0	
27 days	68.5	80	55	++	....	
31 days	64.7	100	60	+	13.6	
44 days	68.1	112	60	+	....	
53 days	73.5	108	..	..	12.7	
65 days	70.6	76	..	..	13.8	
70 days	70.0	112	..	..	13.7	Killed; autopsy performed
Percentage of change	−5%				−15%	

TABLE 2.—*Dog 4*

Time of Examination	Diastolic Area of Heart in X-Ray Plate, Sq. Cm.	Pulse Rate	Running Period, Min.	Fatigue	Weight, Kg.	Comment
Before operation	65.6	96	30	+	16.8	
After operation	55.8	124	..	..	....	
3 days	63.7	...	10	++	....	
4 days	65.4	134	8	+++	....	
5 days	61.5	124	30	++	13.0	
7 days	....	...	28	++	....	
9 days	....	...	60	+	....	
12 days	....	...	50	+	....	
14 days	....	...	45	++	....	
18 days	....	...	55	+	....	
20 days	....	...	30	+	11.6	
24 days	....	...	60	+	....	
30 days	....	...	55	++	10.0	
33 days	....	...	65	+	....	
44 days	59.0	76	..	..	....	
48 days	....	...	60	++	10.0	
53 days	59.9	80	..	..	10.5	
63 days	....	...	..	..	10.0	
65 days	61.9	96	..	..	....	
76 days	....	...	60	+	11.6	
80 days	62.5	92	..	..	....	
91 days	....	...	..	..	13.0	
97 days	54.4	104	..	..	12.0	
98 days	....	...	..	..	....	Killed; autopsy performed
Percentage of change	−15%				−29%	

sacrificed, and autopsy showed extensive noninfectious pericardial adhesions extending from the site of the ligation to the apex. The apex was thin (from 2 to 3 mm.) in thickness and was replaced by a fibrous tissue scar, which was clearly demarcated on the endocardium. This scar included the base of the posterior papillary muscle and extended to the base of the anterior papillary muscle.

The second dog (dog 6, table 3) in this group ran sixty minutes on the third day and every two or three days thereafter for three weeks, with no signs of distress. Beginning on the two hundred twenty second postoperative day, rigorous exercise (from seventy to ninety minutes) was again resumed daily for two weeks. At no time was there any evidence of fatigue or other cardiac symptoms. Throughout this period the weight and the general condition had been practically constant, but after the three hundred second day the animal rapidly lost weight, refused food and died in the cage on the three hundred nineteenth day. Firm adhesions over the entire distribution of the ramus descendens anterior were found at autopsy. Near the apex anteriorly the ventricular muscle was replaced by markedly thinned fibrous tissue (3 by 4 cm.

TABLE 3.—*Dog 6*

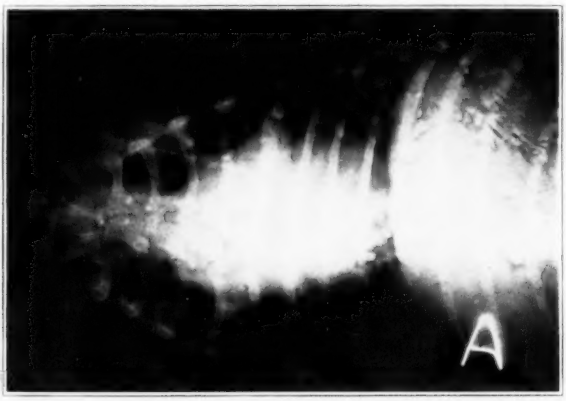
Time of Examination	Diastolic Area of Heart in X-Ray Plate, Sq. Cm.	Pulse Rate	Running Period, Min.	Fatigue	Weight, Kg.
Before operation	54.6	84	50	+	10.6
After operation	*	...	..	..	....
3 days	55.0	108	60	+	....
12 days	53.0	76	60	+	....
17 days	52.0	108	65	+	9.7
30 days	54.8	116	..	..	....
39 days	56.2	84	..	..	....
52 days	54.7	80	..	..	....
67 days	55.4	96	..	..	11.0
78 days	55.6	116	..	..	12.7
84 days	53.6	112	..	..	11.7
96 days	52.9	108	..	..	10.5
109 days	47.0	116	..	..	10.0
222 days	52.0	108	90	+	9.7
236 days	46.1	108	60	+	....
250 days	47.4	124	..	..	9.0
311 days	43.8	126	..	..	7.0
Percentage of change	−20%				−34%

* No film taken.

in thickness), forming a well defined scar. There was no suggestion of an aneurysm from the outside, nor from the x-ray pictures, but on section this thinned area showed a well defined aneurysmal sac. The ramus descendens anterior was completely obliterated in a mass of adhesions at the site of the ligation. One x-ray picture of this dog (see figure) showed bulging at the apex, which was interpreted as an aneurysmal bulging.

In the third group of two dogs, exercise on the treadmill was started on the second day following the operation and continued for forty-five and fifty minutes, respectively. These dogs ran almost daily for periods of from forty-five to seventy minutes for the first three weeks. On the eighth day one dog had a severe attack, giving every indication of undergoing extreme pain. Exercise on the following day again caused a similar attack, but this condition could not be produced

again. This animal died in the cage on the hundred thirty-fifth day, and extensive adhesions were found over the anterior surface of the heart. There was a clearly defined area of fibrosis demonstrable in the endocardium near the apex, including a part of the base of the posterior papillary muscle and some of the anterior papillary muscle. This area was 25 mm. in width by 30 mm. in length and from 1 to 2 mm. in thickness. Although no bulging was noticed in the intact heart, on sectioning there was a definite outpouching of the endocardium. The second dog in this group died after the thirtieth day, unfortunately, no autopsy was done.



X-ray picture of dog 6 showing thinning and bulging of the apex.

COMMENT

The amount of work that the average laboratory dog can perform until exhausted on the treadmill is variable. Previous training and psychic factors probably play an important rôle. From thirty to sixty minutes of running on our treadmill never appeared to cause any appreciable fatigue in the dogs in this series. Subsequent work has shown that a normal dog can run the entire afternoon with only a five minute rest period per hour.

The estimation of fatigue is purely an arbitrary matter. The ease with which the animal exercised before operation was compared with the postoperative runs. The dog having the six days' rest (dog 2) was not exercised severely as to the length of the runs or as to their frequency.

The extensive anastomosis of the superficial coronary arteries can be seen quite easily just under the epicardium of the left venrticle. Miller

and Matthews,[2] Karsner and Dwyer [9] and others have pointed out that because of this extensive anastomosis the scar resulting from ligation is much smaller than the area supplied by the ligated artery. Our findings are in agreement with this statement, the myocardial scar varying greatly as to size even though all the ligations were approximately at the same level. We wish to emphasize the consistent occurrence of anastomosing vessels on the left ventricle between the descending branches of the circumflex and the lateral twigs from the ramus descendens anterior. Thus it is often necessary to ligate one of these anastomosing vessels also in order to obtain a good-sized scar. This extensive anastomosis prevents the formation of a large scar and makes possible a better functional recovery following ligation.

It is frequently stated that exercise increases the work of the heart, and that this leads to hypertrophy. The literature contains considerable evidence supporting the theory of work hypertrophy and some evidence denying it. Our observations show that the body weight and adhesive

TABLE 4.—*Relation of Cardiac Area and Body Weight in This Series of Dogs*

Dog	Change in Cardiac Area	Change in Body Weight	Days Lived
2	5% decrease	15% decrease	70
4	15% decrease	29% decrease	98
6	20% decrease	34% decrease	319
12	1% increase	7% decrease	23
13	9% increase	3% decrease	135

pericarditis are two factors of prime importance, which must be controlled before any conclusions can be drawn concerning the occurrence of cardiac hypertrophy following the ligation of the ramus descendens anterior.

Table 4 shows that in two cases the increase in cardiac area was slight. Stewart [10] and Eyster [11] stated that a variation of more than 10 per cent must occur before one should conclude that there is any real change in the size of the heart. The three remaining dogs showed a decrease in cardiac area each of which was accompanied by a distinct fall in body weight. Simonds and Brandes [12] recently found that in starvation the heart loses weight in about the same proportion as the body as a whole. If we assume from this that there may also be a decrease in the cardiac area, we have evidence in three cases at least that there is a similar decrease in cardiac area with a loss in body weight.

9. Karsner, H. T., and Dwyer, J. E.: J. M. Research **34**:21, 1916.

10. Stewart, H. J.: J. Clin. Investigation **7**:339, 1929.

11. Eyster, J. A. E.; Meek, W. J., and Hodges, F. J.: Cardiac Changes Subsequent to Experimental Aortic Lesions, Arch. Int. Med. **39**:536 (April) 1927.

12. Simonds, J. P., and Brandes, W. W.: Effect of Experimental Hyperthyroidism and of Inanition on Heart, Liver and Kidneys, Arch. Path. **9**:445 (Feb.) 1930.

In this series there was no marked enlargement of the pathologic heart resulting from exercise (table 4). At the beginning of this work it was thought that the formation of a large scar in the myocardium per se might result in cardiac hypertrophy because of the extra load thrown on the remaining healthy cardiac tissue. Regardless of this and the additional work to which these hearts were subjected by exercising, the results do not appear to favor this point of view. It is evident that the body weight must be kept constant throughout the experiment before one can conclude that there is any change in cardiac area due to hypertrophy as determined from the x-ray photograph.

Adhesive pericarditis was a constant finding at autopsy, and this has been presumed to be a causative factor in producing cardiac hypertrophy. Thus, there are two factors, exercise and adhesions, which may play a rôle in producing hypertrophy, while the loss of body

TABLE 5.—*Changes in Cardiac Area in Dogs During Ether Anesthesia*

Dog	Time		Cardia Area, Sq. Cm.	Pulse Rate	Decrease, per Cent
E-1	1:45	Normal	52.9	92	
	2:00	Started ether			
	2:30	During ether	46.1	120	
	2:40	Stopped ether			
	2:50	X-ray	45.8	128	14
	4:10	X-ray	50.0	100	
	48 hr. later	X-ray	50.0	96	
E-2	....	Normal	49.2	120	15
		After	41.9	144	

weight, on the other hand, may cause an actual decrease in the size of the heart.

Effect of Ether and Operations on Size of Heart.—It was noted that several times there was a decrease in the cardiac area immediately following the operation. Stewart [10] advanced several explanations to account for this, among which tachycardia, reflex and direct stimulation of the heart, increase in the vascular bed and diminution of the blood volume are to be considered. The rôle that ether as an anesthetic plays in causing the aforementioned mechanism was investigated by anesthetizing two normal dogs and following the changes in the cardiac area.

It is questionable whether we can attribute any postoperative change in cardiac area to handling or ligating the coronary arteries themselves.

SUMMARY

A rest period of six days after infarction resulted in a small, well contracted scar without thinning of the ventricular wall in one dog.

In the remainder, exercise, within three days after operation, resulted in thin scars with aneurysmal bulging.

Although there is some variation in the x-ray silhouette from time to time, it is noted that the final average shows no evidence of hypertrophy or of dilatation.

Adhesive pericarditis did not cause hypertrophy.

Ether alone apparently causes a decrease in the cardiac area for several hours.

CONCLUSIONS

Apparently rest after myocardial infarction results in the production of a small, firm scar, while early exercise results in a thin, bulging scar. The hope was entertained of proving this more definitely as a clinical fact, but evidently the reserve of a normal young dog's heart is infinitely greater than that of an arteriosclerotic heart.

Myocardial infarction per se does not cause hypertrophy.

Dr. A. C. Ivy gave assistance and encouragement in this work.

PRIMARY CARCINOMA OF THE LUNGS

PATHOGNOMONIC SIGNS IN THE DIAGNOSIS *

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The diagnosis of carcinoma of the lungs still constitutes to the practicing physician a baffling situation with which he is inadequately prepared to grapple. The general practitioner must have, if he is to succeed diagnostically, some definite signs or a definitely pathognomonic symptom complex to go by: in meningitis, the headache, the Kernig sign and the rigidity of the neck; in pneumonia, the respiratory grunt and the peculiar disturbance in the pulse: respiration ratio; in typhoid, the leukopenia, the rose spots and the slow pulse. One can enumerate ever so many other conditions that have become diagnosable by the general practitioner because of the definite pathognomonic signs that they offer.

To these diagnosable conditions more and more disease entities are added as more and more pathognomonic signs and symptoms are elicited as time goes on. To the many conditions that as yet offer to the practitioner nothing fairly pathognomonic belongs carcinoma of the lungs. I have gathered this impression from my personal experience as well as from a careful perusal of the literature on the subject.

In 1904, Sehrt [1] compiled from the literature 210 cases, of which only 6 were diagnosed during life. In 1923, Wells [2] found in Cook County Hospital 11 cases of primary carcinoma of the lungs with only one correct diagnosis. In 1925, Kilkuth [3] found that at the Eppendorf Hospital in Hamburg only 34 per cent of 246 cases were diagnosed during life. As late at 1927, Fried [4] had the following to say:

> In primary carcinoma of the lungs signs are amazingly scant as compared with the amount of tissue involved and the grave character of the lesion. Again often they are ambiguous. . . . Indeed, there is not a single symptom or a group of

* Submitted for publication, March 9, 1931.

* From the Department of Medicine of the Newark Beth Israel Hospital.

1. Sehrt: Beitrag zur Kenntnis der primären Lungencarcinom, Inaugural Dissertation, Leipzig, 1904.

2. Wells, H. G.: Relation of Clinical Diagnosis of Cancer and Value of Existing Cancer Statistics to Necropsy, J. A. M. A. **80**:737 (March 17) 1923; Cancer Statistics as They Appear to Pathologists, ibid. **88**:399 (Feb. 5) and 476 (Feb. 12) 1927.

3. Kilkuth, W.: Ueber Lungencarcinoma, Virchows Arch. f. path. Anat. **225**:107, 1925.

4. Fried, B. M.: Primary Carcinoma of the Lungs, Arch. Int. Med. **40**:340 (Sept.) 1927.

symptoms which is not common to tuberculosis as well as to cancer, or other chronic pulmonary conditions. . . . In brief, it appears that there is no clinical signs which taken alone, would make the diagnosis of a primary neoplasm in the lung certain.

The rate of incidence of primary carcinoma of the lungs is on the increase, which according to the consensus, is actual and not merely due to the greater frequency in the diagnosis. This fact is borne out by the autopsy observations of many eminent pathologists both here and abroad. So little definite is as yet known concerning the possible cause of the increase that it is futile to go into the various theories advanced.

According to Kilkuth,[3] whose necropsy material extended over a period of thirty-five years (1889-1923), primary carcinoma of the lungs represented 9.5 per cent of all the cases of carcinoma in the pathologic institute of the Hamburg Eppendorf Hospital. In 1923, the number of cases of pulmonary carcinoma equalled one-third the number of cases of carcinoma of the stomach found at autopsy at his large institution. In spite of this increasing incidence of pulmonary carcinoma, Fishberg [5] stated that 80 per cent of his patients were sent in with the diagnosis of other pulmonary diseases, even though most of them were observed in other hospitals before admission to the institution with which he is affiliated. The same author insisted, though, that a diagnosis can be made by a careful history and physical examination, and that a very skilful percussion will reveal to the expert ear the fine distinction between the dulness of massive tuberculous involvement and the flatness of carcinoma. He also stated that the amphoric breathing audible in cavernous tuberculosis is usually heard in the mammary region or over the supraspinous region, while in carcinoma with a cavity it is heard over the sternum or the interscapular area. It has been my experience, though, that tuberculous cavities respect no area, while they may favor some. There is no question that the very skillful clinician may, possibly, differentiate between extreme dulness and flatness, and thus may make a diagnosis when others fail. But what about the average general practitioner who must have something more tangible, more pathognomonic? Can the diagnosis of carcinoma of the lungs be made within reach of the rank and file?

In a previous communication,[6] I described a pathognomonic symptom complex that can be elicited, wholly or in part, in the vast majority of cases of primary pulmonary carcinoma. This symptom complex consists of a peculiarly characteristic history and definite physical signs.

5. Fishberg, M.: Diagnosis of Pulmonary Neoplasm, Arch. Int. Med. **37**: 745 (June) 1926.

6. Polevski, J.: Diagnosis of Primary Carcinoma of the Bronchus, M. J. & Rec. **129**:448 (April 17) 1929.

The eliciting of this complex, in my opinion, will enable the average practitioner, in a large majority of cases, to arrive at a correct diagnosis. Of the 6 consecutively diagnosed cases to be described, 2 were diagnosed by the intern.

CHARACTERISTIC HISTORY

In cases of carcinoma, if uncomplicated by coexisting tuberculosis, which situation prevails in many cases, the following is the history. The patient of cancer age, frequently of suggestive appearance, most often states that up to a reasonably short period of time prior to his present complaint he has not been troubled with any pulmonary difficulty. Dr. James F. Percy [7] of Los Angeles, who has had a vast experience with cancer, emphasized further this strikingly negative previous history of patients with cancer. In his experience, these cases evince a history that is unusually free from previous infection in any part of the body.

The condition is ushered in, as far as the patient is concerned, in numerous yet characteristic ways. Some patients state that since an attack of bronchitis or pneumonia, which affected them from a few months to two years prior to their visit to the office, they have never been well, but have, more or less continuously, suffered from some pulmonary difficulty. Some patients state that they have had more than one attack of pneumonia, which has recurred at very short intervals within recent date. This last history is very suggestive. "As the rule is once pneumonia in pulmonary carcinoma always pneumonia for obvious reasons." [8]

In some cases the condition sets in more insidiously, until the more severe symptoms prompt the patient to seek medical advice.

Pain is the most frequently elicited complaint, and more than any other symptom draws the attention of the patient to his condition.

Hemorrhage is not uncommon. It may occur without warning or may develop insidiously.

Dyspnea, next to pain, is the most frequent complaint that brings these patients to the physician. This, too, may develop gradually or may occur suddenly. Occasionally it is ushered in in the form of an asthmatic paroxysm. It may be caused by the final plugging of a bronchus, by the frequently complicating pleural effusion or by a unilateral phrenic paralysis with the resultant partial pulmonary collapse.

Any or all of these complaints in a patient of cancer age, particularly with a negative pulmonary history up to that age, are extremely suggestive and are frequently sufficient to justify a tentative diagnosis of primary pulmonary carcinoma.

7. From a personal conversation with Dr. James Percy.
8. Statement made by Professor Erdheim of Vienna.

The characteristic physical signs consist of:

a. A high position of the diaphragm on the affected side.

b. Paradoxical respiration with a seesaw movement of the diaphragm.

c. Pendulum movement of the heart, which is drawn over to the side affected during inspiration, and away from it during expiration.

d. Frequent coalescence of an area of flatness in the infraclavicular area with the substernal area of cardiac dulness.

For a more detailed explanation of these physical signs, the reader is referred to an article that I published on a previous occasion.[6]

I may state here that in a considerable number of cases all these signs as well as the characteristic history are obtainable, in which case the diagnosis is fairly certain. In some cases the picture may not be complete, in which case a roentgen film, or better still, fluoroscopy, may elicit all the physical signs.

The reason for the absence of some of the characteristic features that are usually present in this condition becomes clear when one thinks of the evolution of its physiopathology; that is, the high diaphragm that is frequently found and the paradoxical respiration are due to the paralysis of the adjoining phrenic nerve. In the early stage of carcinoma of the bronchus or even in later stages, if the mass first develops quite distally to the root and hence away from the phrenic nerve, there may be no paralysis and hence no high diaphragm or paradoxical respiration.

The following is an account of 6 cases diagnosed consecutively in my service in the ward during a period of one year. As stated, 2 of these cases were diagnosed by the intern by applying himself to my method. Two of these cases were verified by autopsy findings. In 3 cases bronchoscopy was performed, and in 2, biopsy material showed carcinoma.

REPORT OF CASES

Case 1.—M. S., a white man, aged 51, a carpenter, gave an essentially negative family history. He had never complained of a pulmonary difficulty up to three years prior to his admission to the hospital, when he first began to be troubled by a slight cough. This, however, did not prevent him from attending to his work. Three months before admission his cough became very annoying, and he experienced severe pain in the chest. Since then he could not work and had lost 25 pounds (11.3 Kg.). He was sent to the hospital by his family physician with the diagnosis of pulmonary tuberculosis.

The age and negative pulmonary history up to the present complaint immediately suggested the possibility of a pulmonary malignant condition. Physical examination revealed the cardiac pendulum phenomenon. The diaphragm, however, was not of the high standing type. Infraclavicular dulness was fused with retrosternal cardiac dulness. A diagnosis of carcinoma of the lung was made. Fluoroscopy revealed a dense shadow in the upper lobe of the left lung. After the patient's first week in the hospital, the cough became very severe and profusely

productive. Physical signs of a cavity soon became apparent. This cavity grew rapidly larger. His expectoration became more profuse and foul. The patient died following a very severe pulmonary hemorrhage. Autopsy revealed a cavity the size of a fist lined by a very ragged, degenerated wall external to which was a grayish-white shell of cartilaginous consistency typical of carcinoma.

CASE 2.—I. W., a white man, aged 70, had an essentially unimportant family history. He could not reveal any previous serious illness. Eight days prior to his call at the office, he was suddenly taken with an attack of dyspnea, which continued practically without interruption. There was also a sensation of unbearable retrosternal pressure. The family physician diagnosed the condition as a severe paroxysm of asthma.

Fig. 1 (case 1).—Primary carcinoma of the left lung.

Examination revealed a mild degree of cyanosis and an expression of extreme alarm. There was an area of flatness in the right interscapular space. The diaphragm on that side was not high, and no paradoxical respiration was made out. The blood pressure was 200 systolic and 110 diastolic. An electrocardiogram, however, failed to reveal any evidence of myocardial changes or anything suggestive of a coronary lesion.

A tentative diagnosis of a neoplasm, either mediastinal or pulmonary, was made on the basis of the previous negative pulmonary history, the interscapular flatness and the intensity of the symptoms.

An x-ray film was very suggestive of a tumor beginning at the bifurcation of the larger right bronchus. The subsequent pain necessitated the constant administration of moderate doses of opiates.

Fig. 2 (case 1).—Small cavity, with the fluid level definitely visible in the upper part of the shadow.

Fig. 3 (case 1).—Very large cavity; irregular masses projecting into it are definitely discernible. It is interesting to observe that, while the cancer cavity in its early stage looks very much like an ordinary abscess with its usual fluid level, as it grows larger the cancerous characteristics become evident. The wall is irregular and is studded with irregular masses.

Examination three weeks later revealed a very high diaphragm on the affected side. No fluid was made out. Paradoxical respiration and a resultant seesaw movement of the diaphragm were elicited. A pendulum movement of the heart was questionable by the percussion method, but was clearly made out by the aid of the fluoroscope. A definite diagnosis was then made of primary bronchial carcinoma of the lung.

The dyspnea continued. The pain, however, abated somewhat. The patient died within six weeks after the first examination in a state of extreme dyspnea and exhaustion. No autopsy was performed, but biopsy material obtained by the bronchoscope revealed carcinoma in the lower part of the right bronchus.

CASE 3.—R. D., a white man, aged 50, gave an irrelevant family history. There was a previous history of pneumonia one and one-half years before examination, up to which time he had never been sick. He had lost 33 pounds (15 Kg.) in

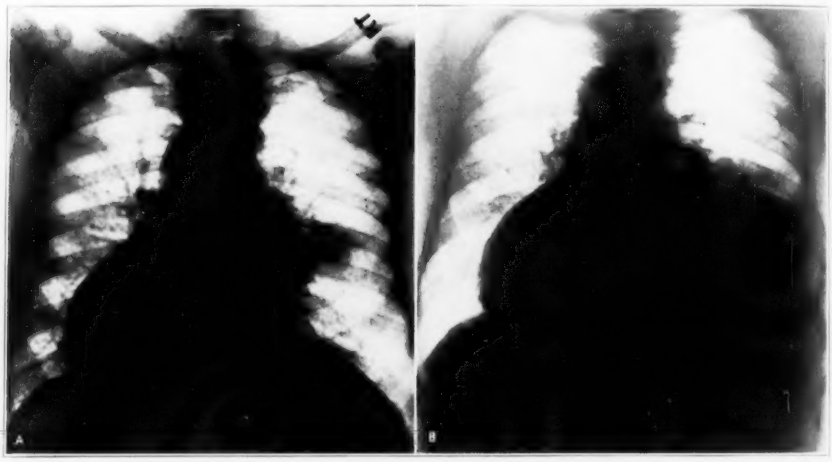

Fig. 4 (case 2).—*A*, chest of patient. *B*, chest three weeks later. The diaphragm is high owing to paralysis of the phrenic nerve and a possible collapse of the lower lobe.

the last seven months. He had continued working up to four months before examination, when he began to tire on slight effort. Since then he had also been suffering from dyspnea, which was constant and was not relieved by rest. He applied at that time for medical aid to a very reputable institution. Evidently carcinoma was then suspected, as bronchoscopy was performed at the institution, though with negative results. An axillary gland was also removed at the same institution for biopsy and was found negative for carcinoma. One month later the patient was tapped by his family physician for a pleural effusion. This gave him temporary relief. Shortly afterward dyspnea recurred, and three months after the tap he applied to my service because of his dyspnea and loss of weight.

Physical examination revealed the following: The right side of the chest was flat from the apex to the base, anteriorly as well as posteriorly. Because of the history, a tentative diagnosis of carcinoma of the lungs was made. After aspira-

tion of the fluid, which was serous, the high position of the diaphragm, the paradoxical respiration, the pendulum movement of the heart and fusion of the right upper dull area with the upper sternal cardiac dulness were made out clinically and corroborated by the fluoroscope. The patient presently refused food, became moribund and died from inanition.

At autopsy, a carcinoma involving the upper lobe of the right lung, extending from the right upper bronchus, surrounded by a large area of atelectasis, was found.

CASE 4.—B. S., a white man, aged 62, gave the following history: Two years before examination he had had a bad cold that confined him to bed for six weeks. The cough had persisted for about one year. A condition then developed

Fig. 5 (case 3).—The upper shadow represents carcinoma and atelectasis of the upper lobe of the right lung. The diaphragm is extremely high.

that was diagnosed as asthma. This was shortly followed by a pleural effusion. He had been unable to work since. His chief complaints on admission were pain in the left side of the chest, loss of weight and hemoptysis.

Examination revealed unilateral left exophthalmos. The left pupil was dilated. The left side of the chest was flat on percussion from the apex to the base. After draining a large amount of serous pleural fluid, the characteristic diaphragmatic phenomena and the pendulum movement of the heart could be clearly made out clinically and fluoroscopically. The upward inspiratory excursion of the left side of the diaphragm was very marked. A diagnosis of primary carcinoma of the left lung was made. Bronchoscopy revealed a mass protruding into the lumen below the bifurcation of the left main bronchus. Biopsy was not made.

The patient left the hospital; he died at home from a severe pulmonary hemorrhage.

Fig. 6 (case 4).—*A*, chest of patient. *B*, chest after the pleural fluid had been drained.

Fig. 7 (case 5).—The shadow represents the tumor and the atelectatic lung.

CASE 5.—B. Z., a white man, aged 48, was never sick until a month prior to his admission to the hospital, at which time he started to cough, with a good deal of mucopurulent expectoration which presently became tinged with blood. The patient had pronounced alcoholism. The sputum was repeatedly negative for tubercle bacilli, and the Wassermann reaction of the blood was negative. The patient was sent to the hospital by his family physician with a diagnosis of advanced pulmonary tuberculosis.

Examination revealed a very emaciated person. The upper right side of the chest was extremely flat, chiefly anteriorly. This area of flatness fused with the upper retrosternal cardiac area. A pendulum movement of the heart could be

Fig. 8 (case 6).—The growth seems to be located peripherally. There is evidence of upper pulmonary collapse and a high diaphragm.

made out definitely. Diaphragmatic excursion was very limited, but was not paradoxical. A diagnosis of pulmonary carcinoma was made. Bronchoscopy revealed the upper part of the right bronchus partly obstructed by a mass that bled readily. No material was obtained for biopsy. The patient left the hospital and was lost from observation.

CASE 6.—Mrs. M. S., a white woman, aged 60, insisted that she had had a negative pulmonary history up to two years before admission to the hospital, since which time she had been suffering from a mild bronchitis. One year before admission she began to cough severely and experienced intense pain in the right side of the chest. She lost her appetite and weight.

Physical examination revealed extreme flatness over the upper right side of the chest which fused with the upper sternal cardiac dulness. A distinct pendulum movement of the heart, a high diaphragm and paradoxical respiration were clearly made out by percussion and were verified by the fluoroscope. A diagnosis of primary pulmonary carcinoma of the right lung was made. Bronchoscopy was not considered essential. Symptoms of pressure on the superior vena cava—facial swelling and puffiness of the arms—recently developed. The patient was still under observation.

Fig. 9 (case 1).—The lung, showing a rugged shell of carcinoma in the upper lobe, with a large irregular cavity.

COMMENT

An analysis of the 6 cases shows that pain occurred in 4, effusion in 2, asthmatic symptoms in 2, hemoptysis in 4, a pendulum movement of the heart in all 6, paradoxical respiration in 4, a high diaphragm in 4, fusion of the upper area of flatness with cardiac dulness in 4, cavity formation in 1, pressure on the sympathicus in 1 and terminal pressure on the superior vena cava in 1.

SUMMARY

1. Primary pulmonary carcinoma can be diagnosed clinically.

2. A characteristic history is obtained in the vast majority of cases.

3. A characteristic complex of physical signs has been described.

4. The fluoroscope is of great aid in doubtful cases and helps to confirm clinically established ones.

5. Bronchoscopy and biopsy are rarely necessary to establish a diagnosis.

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THE USE OF AMIDOPYRINE IN RHEUMATIC FEVER *

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In the treatment of patients with rheumatic fever during the past year in this hospital it has been found that amidopyrine is decidedly superior to other drugs heretofore employed, namely, sodium salicylate, acetylsalicylic acid, the ethyl ester of phenylcinchoninic acid, cinchophen and neocinchophen.[1] As an adequate summary of the properties of amidopyrine is not available elsewhere, a brief review of the literature concerning it is presented as a preliminary to an account of the observations presented in this paper on rheumatic fever.

REVIEW OF THE LITERATURE

Filehne,[2] in 1896 and in 1897, described the synthesis, the properties and a few preliminary therapeutic trials of an antipyretic and analgesic which he arbitrarily named "pyramidon," but which he designated more accurately as 4-di-methyl amino-antipyrine. Antipyrine, a condensation product of methyl-phenyl hydrazine and aceto-acetic ester, was first converted by Stolz,[3] in 1893, into amidopyrine, or pyramidon, by substituting a di-methyl group in the fourth position.[4] Isometric forms of the compound have been described.[5]

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* From the Hospital of the Rockefeller Institute for Medical Research.

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5. Kobert, R.: Beiträge zur Kenntnis einiger Pyrazolonderivate, Ztschr. f. klin. Med. **62**:57, 1907.

The chemical and physical properties have been studied in some detail,[6] and many color reactions have been devised for identification.[7] Amidopyrine is a yellow-white, almost tasteless, crystalline powder, readily soluble in water (1:10) and faintly alkaline in solution. The compound is very susceptible to the action of oxydases, and for this reason certain pharmacologic combinations are contraindicated.[8]

The drug is rapidly absorbed and excreted. After moderate doses by mouth, it appears in the blood and urine within twenty minutes;[9] the urine remains free from detectable traces after two hours. The rapidity of excretion is also demonstrated by the fact that 300 per cent of the intravenous fatal dose may be given to cats by the administration of fractions of the total quantity over a period of twenty-four hours.[9] Although readily decomposed in the body, for only 1 per cent appears unchanged in the urine, the site of destruction has not been identified.[10] The compound is eliminated in the urine chiefly as uraminoantipyrine, in combination with glycuronic acid, and in certain persons as an unidentified complex derivative which readily oxidizes to rubizonic acid, thereby imparting a pink color to the urine.[11] Apert[12] observed such urinary color change, usually beginning four hours after a dose

6. Filehne (footnote 2, first reference). Cushny, Arthur R.: A Text-Book of Pharmacology and Therapeutics, ed. 7, Philadelphia, Lea & Febiger, 1918, p. 473. Meyer, H. H., and Gottlieb, R.: Experimentelle Pharmakologie als Grundlage der Arzneibehandlung, ed. 5, Berlin, Urban & Schwarzenberg, 1921, p. 542.

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12. Apert, E.: Les urines rouges dans la médication par le pyramidon, Arch. auftretenden roten Farbstoff, Therap. Monatschr. **14**:298, 1900. Leick, Bruno: gén. de méd. **2**:1665, 1904.

of 1 Gm., as a peculiar response in about one third of his patients who were receiving therapeutic doses, although no correlation was established with any other unusual reaction to the drug.

The mechanism of antipyresis has not been studied in much detail. There is great increase in heat loss as measured in the calorimeter.[13] This is occasioned by peripheral vasodilatation and increased perspiration, thought to be due to a central action of the drug. It occurs after small doses in febrile, and after large doses in normal, animals. Although heat production is slightly decreased,[14] tissue oxidation is depressed less than in the instance of other antipyretics.[15] Therapeutic doses have a very slight effect on the temperature of normal man,[16] but large doses frequently have been observed to reduce the temperature in afebrile animals.[17]

The analgesic effect is thought to reside in a direct action on the thalamus.[18]

In the earlier French literature, one frequently encounters the statement that amidopyrine generally accelerates metabolism, because a relatively increased excretion of urinary nitrogen as urea was observed during medication.[19] This conclusion seems questionable on such slender evidence, although it is possible that the results quoted may have been associated with altered kidney excretory function similar to that demonstrated more recently in the instance of other antipyretics.[20] Inconclusive studies have been made of the effect of the drug on oxygen

13. Filehne (footnote 2, second reference). Gessler, H.: Ueber den Einfluss des Pyramidons auf den Stoffwechsel, Arch. f. exper. Path. u. Pharmakol. **98**: 257, 1923.

14. Gessler (footnote 13, second reference).

15. Nitzescu, I. I., and Cosma, I.: L'action de quelques antipyrétiques sur la respiration des tissus, Compt. rend. Soc. de biol. **89**:1406, 1923.

16. Filehne (footnote 2, second reference). Blanc, A.: Étude thérapeutique sur le pyramidon, Thèse de Paris, 1903. Holló, Julius: Die Beeinflüssbarkeit subfebriler Temperaturen durch Pyramidon, Wien. klin. Wchnschr. **42**:369, 1929.

17. Filehne (footnote 2, second reference). Klatt (footnote 3). Lépine, R.: Sur la valeur clinique du pyramidon, Lyon méd. **85**:215, 1897.

18. Hoff, H., and Wermer, P.: Klinische Untersuchungen über den Angriffs-Punkt der Analgetica, Klin. Wchnschr. **8**:488, 1929.

19. Blanc (footnote 16, second reference). Bertherand, L.: Contribution à l'étude du pyramidon et de ses sels, Bull. gén. de thérap. **141**:243, 1901; **142**: 276, 1901. Bardet, G.: Action antithermique du pyramidon, Bull.gén.de thérap. **141**:367, 1901. Robin, Albert, and Bardet, G.: Un médicament aromatique, analgesique, et antipyrétique excitateur des échanges organiques, le diméthyl-amido-antipyrine ou pyramidon, Compt. rend. Cong. internat. de méd., Paris, 1900 (Sect. therap.), p. 137.

20. Myers, V. C., and Killian, J. A.: Studies on the Influence of Phenylcinchoninic Acid and the Ethyl Ester of Paramethylphenyl-Cinchoninic Acid on Renal Excretion, J. Pharmacol. & Exper. Therap. **18**:213, 1921.

consumption and internal respiration.[21] Retention of water and sodium chloride, possibly the result of a central action, have been observed in animals.[22]

There is definite effect on sugar metabolism, in that therapeutic doses lower the blood sugar level slightly in normal men and animals,[23] but increase it in persons with severe diabetes and in depancreatectomized dogs.[24] Very large, toxic doses in animals uniformly cause an increase in the blood sugar.[25] These observations are interpreted as indicating a direct action on the pancreas. Temporarily increased excretion of sugar in diabetic persons has been observed frequently coincident with the administration of amidopyrine.[26]

The general symptoms following varied doses by different routes of administration have been studied extensively in several species of animals.[27] In the dog, 0.2 Gm. per kilogram of body weight by mouth is the usual maximum sublethal dose, and on the basis of comparative weights roughly corresponds with from 8 to 10 Gm. in man.[28]

Miscellaneous studies of the effects of the drug have demonstrated the following: (1) a peripheral action in lowering the tonus of smooth muscle;[29] (2) a depression of the higher centers (an observation of the behavior of rats in a circular maze[30]); (3) a slight elevation of the

21. Robin and Bardet (footnote 19, fourth reference).

22. Gessler (footnote 13, second reference). Averbuck, S. H.: Ueber die Diuresehemmung durch Antipyretika, Arch. f. exper. Path. u. Pharmakol. **157**: 330, 1930.

23. Gessler (footnote 13, second reference). de Carvalho, Alberto: Contribution à l'étude de l'action des antipyrétiques sur la glycémie, Compt. rend. Soc. de biol. **98**:1583, 1928.

24. Chiari, H., and Regler, R.: Zur Frage der Beziehung zwischen Wärme-Regulation und Zuckerstoffwechsel: Die Beeinflüssung des Blutzuckers durch Fiebermittel der Pyrazolongruppe, Ztschr. f. d. ges. exper. Med. **46**:443, 1925.

25. Legendre, Charles: Sur le pyramidon: Étude expérimentale et thérapeutique, Paris, 1897, thèse no. 270. Lépine, R.: Sur le pyramidon, Rev. de méd., Paris **17**:196, 1897.

26. Bertherand (footnote 19, second reference). Robin and Bardet (footnote 19, fourth reference). Henneberg, H.: Eine Migräninvergiftung, Therap. Monatsh. **18**:50, 1904.

27. Filehne (footnote 2, second reference). Blanc (footnote 16, second reference). Lépine (footnote 17, third reference and footnote 25, second reference).

28. Lépine (footnote 17, third reference).

29. Januschke, H., and Lasch, F.: Ueber die periphere Wirkung des Pyramidons: I. Mitteilung: Die Wirkung des Pyramidons auf die glatte Muskulatur, Arch. f. exper. Path. u. Pharmakol. **114**:70, 1926; Ueber die Wirkung des Pyramidons auf die Muskulatur des Darmes, Klin. Wchnschr. **5**:321, 1926. Lasch, F., and Perutz, A.: Pharmakologische Untersuchungen über die Wirkung des Pyramidons auf das Genitale, Arch. f. Dermat. u. Syph. **150**:474, 1926.

30. Macht, D. I., and Bloom, W.: Effect of Some Antipyretics on the Behavior of Rats in the Circular Maze, J. Pharmacol. & Exper. Therap. **17**:21, 1921.

threshold of hearing in man;[31] (4) no effect on muscular coordination,[32] and (5) a capacity of inducing hypersensitiveness in animals which may be passively transferred.[33] With regard to properties that might impair therapeutic value, amidopyrine proved inferior to the other antipyretics and analgesics with which it was compared in these experiments only in the depression of higher cerebral function.

After the introduction of amidopyrine by Filehne in 1896, it was given many clinical trials in a wide variety of diseases, and was most extensively used in typhoid fever.[34]

There were diverse opinions regarding the value of the drug in this disease; but the composite conservative conclusion seems to have been that in instances in which baths are inadvisable by reason of extreme delirium or objection on the part of the patient, and in the presence of great weakness, perforation or bleeding, it may be of use. Amidopyrine in rather small doses (from 0.15 to 0.3 Gm.) frequently repeated was effective as an antipyretic and in clearing the sensorium, but there was occasional vomiting, thought by some observers to be due to the medication. With the disappearance of fever, symptoms of collapse, with weak pulse, profound drop in temperature and cyanosis, some-

31. Macht, D. I.; Greenburg, J., and Isaacs, S.: The Effect of Some Antipyretics on the Acuity of Hearing, J. Pharmacol. & Exper. Therap. **15**:149, 1920.

32. Macht, D. I.; Isaacs, S., and Greenberg, J. P.: On the Influence of Some Antipyretics on the Neuro-Muscular Co-Ordination Test of "Tapping," Proc. Soc. Exper. Biol. & Med. **15**:61, 1918.

33. Biberstein, H.: Beiträge zur passiven Uebertragung der Ueberempfindlichkeit gegen chemisch bekannte Stoffe, Ztschr. f. Immunitätsforsch. u. exper. Therap. **48**:297, 1926.

34. Filehne (footnote 2, first reference). Klatt (footnote 3). Leick (footnote 11, fifth reference). Blanc (footnote 16, second reference). Lépine (footnote 17, third reference). Brandies, A.: Ueber die Behandlung des Typhus abdominalis mit Pyramidon, Prag. med. Wchnschr. **22**:525, 1897. Butters: Ueber Pyramidon, Festschr. z. Eröffn. d. n. Krankenh. d. Stadt Nürnb., 1898, p. 505. Byk, L.: Ueber die Anwendung des Pyramidons bei Typhus abdominalis, Deutsche med. Wchnschr. **29**:51, 1903. Gerest and Rigot: Traitement de la fièvre typhoïde par le pyramidon, Loire méd. **19**:281, 1900. Hirtz: L'observation de plusieurs malades ayant eu une chûte brusque de température après l'injection de doses légères de pyramidon, Bull. et mém. Soc. méd. d. hôp. de Paris **33**:959, 1912. À propos de l'emploi du pyramidon chez les typhiques, Presse méd. **54**: 573, 1912. Hödlmoser, C.: Ueber den Wert des Pyramidons für die Behandlung des Abdominaltyphus, Wien. klin. Wchnschr. **18**:103, 1905. Horneffer, Curt: Pyramidon (Dimethylamidoantipyrin), Berl. klin. Wchnschr. **34**:759, 1897. John, M.: Zur Pyramidonbehandlung des Typhus, München. med. Wchnschr. **59**:987, 1912. von Krannhals, H.: Ueber die Anwendung des Pyramidon beim Abdominaltyphus, München. med. Wchnschr. **51**:2175, 1904. Philibert, A.: Les pérforations intestinales au cours de la fièvre typhoïde, Gaz. d. hôp. **83**:237, 1910. Valentini: Ueber die systematische antifebrile Behandlung des Unterleibstyphus mit Pyramidon, Deutsche med. Wchnschr. **29**:273, 1903.

times occurred. As no other untoward effects of the medication were encountered, the conclusion was reached by some observers that these symptoms were not in the nature of a side action, but rather the direct result of inadvisable lowering of the temperature. In particular, the duration of the febrile phase of the disease and the development of myocarditis were uninfluenced.[35] The ability of the patient to elaborate specific agglutinins was not depressed.[36]

Amidopyrine has also been used in febrile tuberculosis of all forms.[37] Often a complete antipyretic effect was secured; if not, other antipyretics likewise were ineffective. Except for excessive sweating, no untoward reactions were observed in most instances, while appetite was occasionally increased and malaise overcome to a degree apparently beneficial. However, the natural progress of the disease was uninfluenced.

Patients with a variety of febrile diseases, including pneumonia,[38] influenza,[39] bronchitis,[40] erysipelas,[41] scarlet fever,[42] puerperal sepsis,[43]

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35. Widenmann, A.: Pyramidonbehandlung des Unterleibstyphus, Med. Klin. **2**:814, 1906. Remberg, Pierre: Traitement de la fièvre typhoïde par le pyramidon, Nouv. remèdes **19**:438, 1903.

36. Beniasch, M.: Ueber den Einfluss der Antipyrese auf die Agglutinations-Kraft des Blutes beim Abdominaltyphus, Ztschr. f. klin. Med. **45**:51, 1902.

37. Filehne (footnote 2, first reference). Klatt (footnote 3). Blanc (footnote 16, second reference). Bertherand (footnote 19, second reference). Robin and Bardet (footnote 19, fourth reference). Butters (footnote 34, seventh reference). Gerest and Rigot (footnote 34, ninth reference). Horneffer (footnote 34, thirteenth reference). Kétly, L.: Pyramidon, Heilkunde **4**:12, 1899. Blumenthal, A.: Therapeutische Verwendung von Pyramidon und seinen Salzen bei Phthisis pulmonum, Deutsche Aerzte-Ztg., 1901, no. 19, p. 438. Hirschkron, J.: Neuere Erfahrungen mit Pyramidon, Allg. Wien. med. Ztg. **46**:142, 1901. Kobert, R.: Pharmakotherapeutische Rükblicke: II. Die Antipyretica, Deutsche Aerzte-Ztg., 1899, no. 2, p. 30. Lublinsky, W.: Ueber die Wirksamkeit des Pyramidons bei dem Fieber der Phthisiker, Therap. Monatsh. **15**:513, 1901. Müller: Ueber Pyramidon, Deutsche Prax. **12**:680, 1903. Pollak, J.: Einige neue Medicamente in der Phthiseotherapie, Wien. klin. Wchnschr. **13**:59, 1900. Tauszk, F.: Die Salze des Pyramidons, Deutsche Prax. **14**:204, 1905. Roth, D.: Ueber Wirkungsweise des Pyramidons bei verschiedener Krankheitszuständen, Wien. klin. Wchnschr. **10**:964, 1897.

38. Filehne (footnote 2, first reference). Butters (footnote 34, seventh reference). Horneffer (footnote 34, thirteenth reference). Hirschkron (footnote 37, tenth reference). Müller (footnote 37, fourteenth reference).

39. Blanc (footnote 16, second reference). Horneffer (footnote 34, thirteenth reference). Müller (footnote 37, fourteenth reference).

40. Hirschkron (footnote 37, eleventh reference). Müller (footnote 37, fourteenth reference).

41. Filehne (footnote 2, first reference). Blanc (footnote 16, second reference). Butters (footnote 34, seventh reference). Horneffer (footnote 34, thirteenth reference).

42. Filehne (footnote 2, first reference). Horneffer (footnote 34, thirteenth reference).

43. Müller (footnote 37, fourteenth reference).

meningitis,[44] mumps,[45] smallpox,[45] measles [44] and malaria,[46] have been treated with amidopyrine, with effective antipyresis in all except malaria.

In 1903, Müller [43] reported beneficial effects in a number of cases of measles; and more recently,[47] striking abortive and apparently curative properties brought about in this disease by amidopyrine have been observed, although not universally.[48]

Because the antipyretic effects of amidopyrine have been so impressive, it has been proposed on the basis of extensive clinical studies of patients treated for tuberculosis that a temperature not lowered by moderate doses is, in fact, a normal temperature.[49] Interesting effects were observed by Weltmann,[50] who gave single doses of 1 Gm. to patients with subfebrile temperatures following a variety of long and severe infections. In some cases there was only a temporary return of the temperature to normal, indicating a persisting infection; in others the temperature became normal and remained there. Weltmann suggested that in the latter instances the regulating center may have been "set at a higher level" as a result of the long-continued febrile state.

There are occasional, scattered references to a sedative action of amidopyrine. It is probably this property, in addition to a possible influence of therapeutic doses in relaxing smooth muscle, that accounts for a reported beneficial effect in asthma.[51]

Striking examples of the analgesic potency of amidopyrine are reported in the literature.[52] In migraine, tic douloureux, tabetic crises

44. Butters (footnote 34, seventh reference).

45. Blanc (footnote 16, second reference).

46. Roth (footnote 37, seventeenth reference).

47. Loewenthal, Max: Amidopyrin in the Treatment of Measles, Brit. M. J. **2**:51, 1924. Collier, J. I.: Treatment of Measles with Amidopyrin, ibid. **1**:1093, 1930. Ronaldson, G. W., and Collier, J. I.: Amidopyrin in the Treatment of Measles, ibid. **2**:994, 1930.

48. Attlee, W. H. W.: Amidopyrin in the Treatment of Measles, Brit. M. J. **2**:996, 1930.

49. Holló (footnote 16, third reference); Ueber eine neue Methode zur Beurteirlung subfebriler Temperaturkurven im Verlaufe der Lungentuberkulose, Beitr. z. Klin. d. Tuberk. **36**:29, 1916. Mayrhofer, Heinrich: Die Beeinflüssbarkeit subfebriler Temperaturen durch Pyramidon, Wien. klin. Wchnschr. **42**:107, 1929.

50. Weltmann, O.: Ueber den Einfluss einer einmaligen massiven Pyramidon-Dosis auf postinfektiöse Temperatursteigerungen (Pyramidonstoss), Med. Klin. **25**:1659, 1929.

51. Albrecht: Ueber Pyramidon, besonders beim Asthma, Therap. d. Gegenw. **4**:476, 1902.

52. Blanc (footnote 16, second reference). Bertherand (footnote 19, second reference). Robin and Bardet (footnote 19, fourth reference). Hirschkron (footnote 37, eleventh reference). Müller (footnote 47, fourteenth reference). Althausen: Schmerzstillende Wirkung des Pyramidons, Med. Klin. **10**:1498, 1914. Laudenheimer, Rudolf: Ueber Anwendung des Pyramidons bei Nervenkrankheiten, Therap. Monatschr. **12**:177, 1898. von Donat: Pyramidon in der Zahnheilkunde, Deutsche zahnärztl. Wchnschr. **10**:436, 1907.

and other painful diseases, it has often been found effective when other similar drugs have failed, at times even when opiates were insufficient.[53]

The first use of this drug in rheumatic fever was reported by Roth, in 1897.[46] He favored it especially, because there were no undesirable incidental effects, and he was so deeply impressed by the powerful antisymptomatic properties that he proposed a theory of specific action in this disease. During the few succeeding years (from 1897 to 1903), similar observations were continued by Breyer,[54] Robin and Bardet, Pauli,[55] Hirschkron, Bertherand and Müller. All except Bertherand, who reported two failures, confirmed Roth's observations, and considered amidopyrine the drug of choice in the treatment for this disease.

As chemically induced antipyresis generally fell into disfavor, the striking advantages of amidopyrine in the treatment for rheumatic fever seemed to be forgotten. The value of the drug in this connection was accidentally rediscovered by Schottmüller,[56] who reported briefly in 1927, and in more detail in 1929. His assistant, Bodenstab,[57] also reviewed the subject in 1928. They found that therapeutic doses can be given without provoking symptoms of toxicity, and that very few cases are refractory. Instances were cited in which amidopyrine afforded complete relief when symptoms of intoxication enforced discontinuance of sodium salicylate, and when the latter, although tolerated in the usual therapeutic doses, was ineffective. After sodium salicylate had been used almost exclusively for thirty years in the treatment for rheumatic fever in the clinic of Professor Schottmüller, a change was made to amidopyrine. One other recent reference to the value of the drug in rheumatic fever was made by Motzfeldt.[58]

The levels of therapeutic and toxic doses and the relation of the size of the dose to the appearance of untoward effects can be estimated very well from the experiences in the various diseases mentioned.

53. Lépine (footnote 17, third reference). Kohn, S.: Pyramidon und Morphium, Prag. med. Wchnschr. **32**:222, 1907.

54. Breyer, A.: Die praktische Verwerthbarkeit des Pyramidons als fieberwiedrigen und schmerzstillenden Mittels, Inaug. Dissert., Breslau, 1899.

55. Pauli, W.: Ueber Nebenwirkungen des Pyramidons, Centralbl. f. d. ges. Therap. **18**:129, 1900.

56. Schottmüller, H.: Therapeutische Erfahrungen: IV. Behandlung des akuten und chronischen Gelenkrheumatismus mit Pyramidon, München. med. Wchnschr. **74**:861, 1927; Ueber akute Gelenkentzündungen, ihre Aetiologie und Behandlung, ibid. **76**:499, 1929.

57. Bodenstab, Rudolf: Ueber die Behandlung der Polyarthritis rheumatica acuta und chronica mit Pyramidon, Deutsches Arch. f. klin. Med. **159**:171, 1928.

58. Motzfeldt, K.: Salicylates in the Treatment of Rheumatic Fever, Acta med. Scandinav., 1930, supp. 34, p. 8.

The especial instance of typhoid fever, in which symptoms of circulatory collapse sometimes accompany antipyresis, has been discussed in this connection. In the treatment for tuberculosis, the doses were usually small, but from 1 to 2 Gm. was sometimes given daily for months. In miscellaneous febrile diseases similar amounts were effective, but were not continued for long periods. As an analgesic for various pains of nerve origin, small quantities were often sufficient; however, single doses of 1.25 Gm.[59] and daily doses of from 2 to 3 Gm. were given.[60] In rheumatic fever, the earlier observers employed from 1 to 2 Gm., rarely 3 Gm., daily. Müller at one time raised the quantity to 10 Gm., and continued the administration at a level of from 4 to 6 Gm. daily for three months. Schottmüller found that the instances were rare, indeed, in which more than 3 Gm. was required daily, and considered this the maximum therapeutic dose. He found, however, that full therapeutic doses may be continued for months without harm.

Several authors called attention to the remarkable constancy of response in different persons, the absence of habit formation and the fact that there is no increase in tolerance or cumulative effect from long-continued administration.[61] Apert [12] observed that children are tolerant to very large quantities, but other authors recommended smaller doses for them. Loewenthal [62] gave the formula he used with reference to age.

Many observers, regardless of the size of dose used or the disease for which the patient was treated, reported an entire absence of important untoward effects.[63] Others encountered instances of idiosyncrasy or of undesirable incidental reactions in some patients after large doses. As has been noted, symptoms of collapse occasionally followed the use of the drug in typhoid fever. They have been observed in other patients: twice by Neisser [64] (in one instance after a dose of 0.2 Gm.), occasionally by Mesnard [65] in persons with alcoholic delirium or depres-

59. Laudenheimer (footnote 52, seventh reference).

60. Robin and Bardet (footnote 19, fourth reference). Legendre (footnote 25, first reference).

61. Filehne (footnote 2, first reference). Remmets (footnote 11, sixth reference). Horneffer (footnote 34, thirteenth reference). Althausen (footnote 52, sixth reference). Kohn (footnote 53, second reference).

62. Loewenthal (footnote 47, first reference).

63. Klatt (footnote 3). Leick (footnote 11, fifth reference). Remmets (footnote 11, sixth reference). Butters (footnote 34, seventh reference). Gerest and Rigot (footnote 34, ninth reference). Horneffer (footnote 34, thirteenth reference). Valentini (footnote 34, seventeenth reference). Remberg (footnote 35, second reference). Hirschkron (footnote 37, eleventh reference). Pauli (footnote 55).

64. Neisser: Neuere diagnostische und therapeutische Methoden beim Typhus, Berl. klin. Wchnschr. **41**:821, 1904.

65. Mesnard, P. A.: Emploi thérapeutique du pyramidon, Presse méd. **2**:762, 1902.

sion, and once by Blumenthal [66] in a patient severely ill with tuberculosis. Henneberg [67] described vomiting and dizziness in a diabetic patient. Laudenheimer [68] reported that as an analgesic in an afebrile patient, a single dose of 0.4 Gm. caused a complaint of precordial "anxiety," and that in another person the same complaint followed a dose of 1.25 Gm. Schottmüller [69] occasionally observed gastric disturbances on continued daily doses of over 3 Gm. Pauli [55] mentioned one instance of a painful axillary paresthesia after long-continued administration. Mild symptoms, such as weakness, fatigue, malaise, loss of appetite and dizziness, have been reported very rarely, usually following large doses of the drug or in patients in whom such developments might be anticipated incident to their disease. An extensive bibliography with reference to side actions observed in patients was given by Seifert.[70]

Skin manifestations following amidopyrine have been reported only infrequently. Transient purpura, urticaria or erythema have been noted in one or two patients each by three observers.[71] Five more severe reactions [72] (progressing to subcutaneous edema and the formation of bullae), some of them due to a proprietary medicine, "midol," [73] containing amidopyrine, have been described in detail. A few of these patients were sensitive to several coal-tar derivatives.

Attention has also been called to the absence of certain evidences of toxicity that similar coal-tar derivatives may cause in therapeutic doses; there is no deleterious effect on hemoglobin; the normal or diseased kidney is not taxed, and there is no direct depressing effect on the circulation.[74] The absence of symptoms similar to those of salicylism is universally noted.

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66. Blumenthal (footnote 37, tenth reference).

67. Henneberg (footnote 26, third reference).

68. Laudenheimer (footnote 52, seventh reference).

69. Schottmüller (footnote 56, second reference).

70. Seifert, Otto: Die Nebenwirkungen der modernen Arzneimittel, Kabitzsch, Würzburg, 1915.

71. Bertherand (footnote 19, second reference). Gerest and Rigot (footnote 34, ninth reference). Widenmann (footnote 35, first reference).

72. Hallopeau: Sur l'apparition d'exanthèmes identiques après l'ingestion d'antipyrine, d'aspirine et de pyramidon, Bull. Soc. franç. de dermat. et syph. **17**:242, 1906. Reitter, Carl: Exanthem nach Pyramidongebrauch, München. med. Wchnschr. **50**:140, 1903. Zieler: Pyramidonexanthem, Arch. f. Dermat. u. Syph. **86**: 311, 1907. Bechet, Paul E.: Extensive Dermatitis Medicamentosa, Following the Use of Midol (Pyramidon), J. A. M. A. **59**:1289 (Oct. 5) 1912.

73. Editorial: "The Propaganda for Reform": Pyramidon Entering the Patent-Medicine Field—Midol, J. A. M. A. **59**:461 (Aug. 10) 1912.

74. Filehne (footnote 2, first reference). Francis and Fortesque-Brickdale (footnote 4, third reference). Leick (footnote 11, fifth reference). Blanc (footnote 16, second reference). Bertherand (footnote 19, second reference). Remberg (footnote 35, second reference). Kobert (footnote 37, twelfth reference). Kohn (footnote 53, second reference).

Five cases of poisoning have been reported. Single toxic doses of 5 Gm.[75] and 7 Gm.[76] have been survived. Death has occurred after the administration of an unknown quantity,[77] and in two instances half an hour following doses of 30 Gm. taken by mistake.[78] The autopsy observations were negative in each case. A fall in temperature, vomiting, a sense of suffocation and precordial pain, cold sweats, chills, weak and irregular pulse, depressed reflexes and cyanosis, followed by delirium, convulsions and coma, were the usual findings.

EFFECTS OF AMIDOPYRINE OBSERVED IN RHEUMATIC FEVER

All the drugs used in rheumatic fever are effective, probably through purely antisymptomatic properties.[58] They are analgesics, antipyretics and antiphlogistics. With this in mind, a plan of treatment about to be described has been evolved in the hospital of the Rockefeller Institute for Medical Research. The use of one of these agents is indicated in any of the following circumstances: (1) pain or discomfort arising from arthritis, pericarditis or pleurisy; (2) exhausting fever, and (3) extreme "toxicity." The dose is increased until a therapeutic result is secured, the only limitation being evidences of intoxication from the drug. Then, an effort is made to maintain, as it were, a balance between the effects of the disease and the counter-effects of the medication. In other words, after the requisite daily dose is determined, it is lowered slightly from time to time, particularly on any evidence that the disease is less active, in order that the dose may be kept at the lowest level effective. An example of this is demonstrated in chart 1. In the case illustrated in the chart the dose was gradually reduced beginning on May 27, and the drug was discontinued on June 5. There was immediate relapse. A second withdrawal seemed indicated on June 24, but after a slight reduction from the previous level, symptoms reappeared. (The temperature elevation, from July 20 to 25, which was not abated by increased doses of amidopyrine, was thought to be due to the effect of hot weather on a patient with inadequate blood circulation. During the interval indicated, the temperature in this patient's room occasionally rose to 110 F. There were no signs that could be interpreted as indicating a more active infection. Subjectively, there was improvement. A distinct loss in weight is to be noted on the chart.) On a third trial, beginning on September 27, the drug was withdrawn entirely for a few days. It was again required; but for the succeeding two months, 0.6 Gm. daily

75. Dandrieu, P.: Empoisonnement par le pyramidon, guérison, Province méd., Paris **24**:532, 1913.

76. Rotky, H.: Pyramidonvergiftung, Wien. Arch. f. inn. Med. **10**:595, 1925.

77. Geill, Torben: Ein Fall von tödlicher Vergiftung durch Pyramidon, Deutsche Ztschr. f. d. ges. gerichtl. Med. **7**:344, 1926.

78. Prouzerque, Remy: Note sur la diffusion et la localisation du pyramidon, J. de pharm. et chim. **27**:372, 1923.

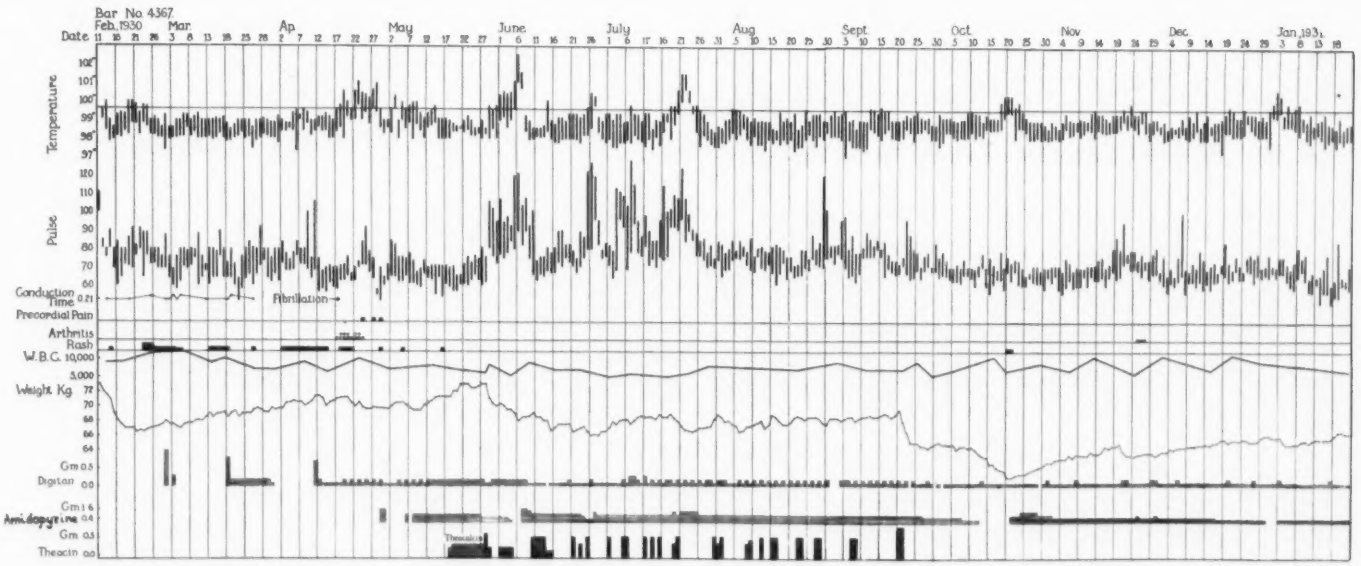

Chart 1.—The course of patient "Bar." during amidopyrine, digitan and theocalcin therapy. Mild arthritis is indicated by small blocks on the appropriate line. Intensity of erythema marginatum is indicated by thickness of line marked "Rash."

was sufficient, whereas during the five months before that, 0.9 Gm. or more was required. After December 16, a dose of 0.3 Gm. kept the patient fever-free, although this small quantity was necessary, as demonstrated after December 31, when it was withdrawn temporarily, and the temperature rose to almost 101 F. in two days. The extent to which the activity of the disease has diminished, and consequently the daily dose necessary for effect, can be determined only by such trials.

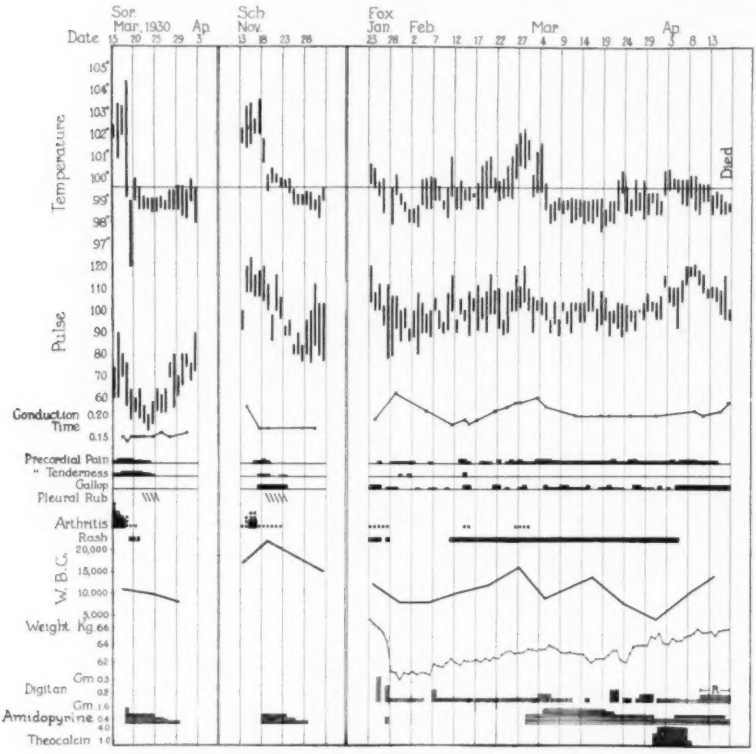

Chart 2.—The course of the infection in three patients during amidopyrine medication. Patient "Fox" also received theocalcin and digitan; for the latter drug, "*R*" indicates rectal administration. Severe arthritis is represented by heavy blocks and mild arthritis by smaller blocks.

During a period of twelve months, amidopyrine was used in this manner in the treatment of thirty-two patients with rheumatic fever. In no instance were the therapeutic results observed to differ from those of other antirheumatic drugs. An analysis of the results yields the following generalizations:

1. Acute attacks of rheumatic fever were relieved by small doses of amidopyrine (from 0.6 to 1.2 Gm. daily), which often were reduced or discontinued within a week. Such response in acute involvement was observed in recurrences (four instances) and associated with carditis, pleurisy or pneumonia (seven instances, including the first two cases demonstrated in chart 2, patients "Sor." and "Sch."). Some patients were severely ill, but small doses effectively relieved the symptoms. The tendency to relapse, however, was apparently not modified by this therapy.

TABLE 1.—*Effects of Amidopyrine on Two Patients with Rheumatic Fever*

Case	Day of Disease	Daily Dose, Amidopyrine, Gm.	Average Temperature Level, F.	Arthritis		
				Pain	Tenderness	Swelling
11	35-38	0.00	103.5	+++*	+++	++
	39	0.90	99.6	++	++	++
	40-41	0.45	—100.0	+	++	++
	42-44	0.45	100.0	—†	—	++
	45-56	0.45	101.0	—	—	—
	57-59	0.45	100.5	—	—	—
	60	0.45	Normal	—	—	—
	61-73	0.45	+100.0	—	—	—
	74-112	0.00	100.0	—	—	—
	210-303	0.00	100.0-101.0	—	—	—
	304-305	0.90	100.0	—	—	—
	306-313	1.50	101.0	—	—	—
	314-380	1.50	100.5	—	—	—
24	6-8	0.00	103.5	++++	++++	++++
	9	0.90	101.8	++	++	++
	10-11	0.90	101.0	—	++	++
	12-13	0.90	100.5	—	+	+
	14-15	0.90	101.0	—	++	—
	16-20	1.20	101.6	—	++	—
	21-24	1.80	102.0	+	++	+
	25-27	1.80	100.5	±	+	+
	28-37	1.80	Normal+	+—	+	+—
	38-43	1.20	—100.0	+—	+	—
	44-51	1.20	100.0	+—	+	—
	52-54	0.90	100.0	+—	+	—
	55-65	0.6-0.3	100.0	—	+	—
	66-68	0.00	100.0	—	+	—
	69-72	0.00	100.5	++	++	++
	73-76	0.90	—100.0	±	+	++
	77-79	0.9-0.6	Normal	—	±	—
	80-94	0.00	Normal	—	±	—

* ± to ++++ = varying degree of intensity.
† — = negative reaction.

2. In chronic or subacute phases of the disease, much larger doses (from 0.9 to 2 Gm. daily) were usually required over longer periods of time. Case 11, table 1, is an example of this. On admission, the patient, who was severely ill, was relieved and his temperature reduced from 103.5 F. to subfebrile levels by doses of 0.45 Gm. of amidopyrine daily. Nine months later, when he was perfectly comfortable, although maintaining a fever of 101 F., 1.5 Gm. daily did not afford complete antipyresis. Such subacute stages of the disease, relatively refractory to the antipyretic influence of the drug, were more often encountered in recurrences (five cases, including those demonstrated in chart 3, patients

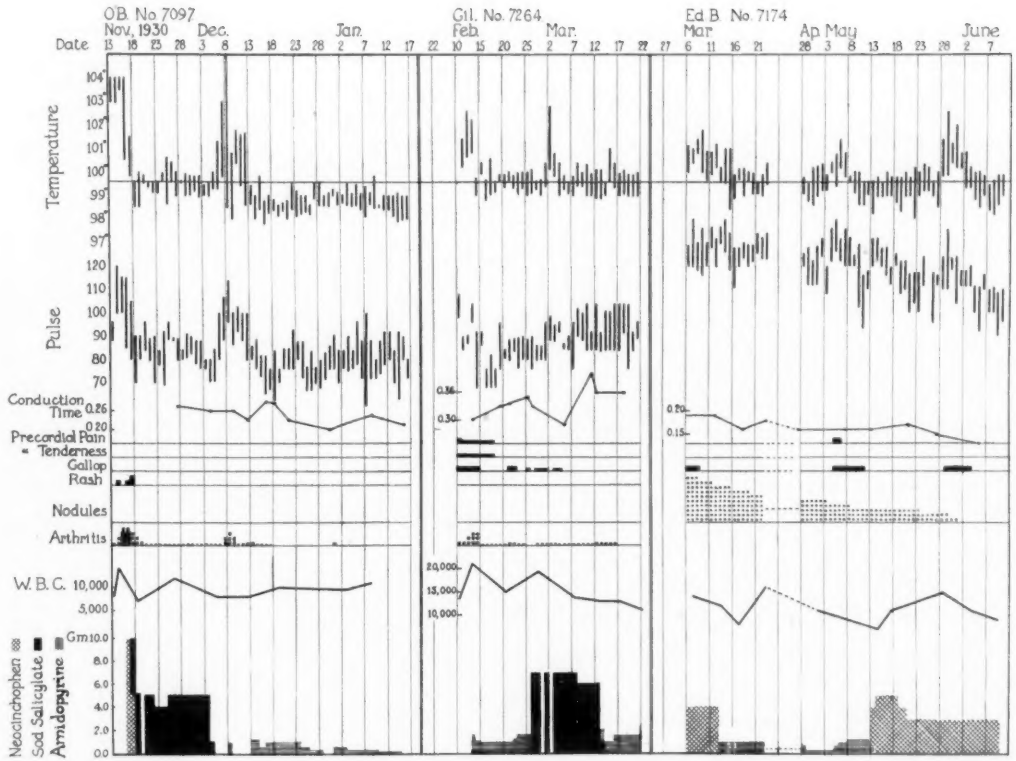

Chart 3.—The course of infection in three patients, all of whom during certain intervals received amidopyrine, and during other intervals, sodium salicylate or neocinchophen. Arthritis is indicated as in chart 2. In the case of "Ed.B." nodules are indicated by solid circles.

"Gil." and "Ed. B.," and in chart 2, patient "Fox"). Fundamentally, however, chronicity was the factor that rendered the patient less amenable to the antipyretic effects of the drug.

3. Tonsillitis, sinusitis and otitis media were observed in several instances concomitant with active rheumatic fever. The temperature elevation due to these infections was less responsive to medication than that exhibited in cycles not so complicated.

4. The effects were definitely restricted to antipyresis, analgesia, the lessening of exudation and, possibly, the relief from symptoms of "toxicity" to a degree unaccounted for by antipyresis. Thus, fever might be abolished and the pulse slowed when acceleration was not a

TABLE 2.—*The Appearance (A), Persistence (P) and Disappearance (D) of Various Evidences of Active Rheumatic Disease While the Patients were Receiving Therapeutic Doses of Amidopyrine*

Case	Rheumatic Erythema Marginatum	Rheumatic Subacute Nodules	Pleural Rub	Gallop Rhythm	Precordial Pain and Tenderness	Pericardial Rub
1	.. .. ..	.. .. ..	.. .. ..	.. .. D	.. .. D	.. .. D
3	.. P ..	.. .. ..	.. .. ..	.. .. ..	.. .. D	.. .. ..
4	.. .. ..	A P ..	.. .. ..	.. .. ..	A .. D	A P ..
7	.. .. ..	.. .. ..	.. .. ..	.. P ..	A P ..	A P ..
8	.. P ..	.. .. ..	.. .. ..	.. .. ..	.. P ..	.. .. ..
10	.. .. ..	.. .. ..	.. .. ..	.. P ..	.. P ..	.. .. ..
11	.. .. ..	.. .. ..	.. .. ..	A .. D	.. .. ..	A .. D
15	A P ..	A P ..	.. .. ..	.. .. ..	.. .. ..	.. .. ..
19	.. .. ..	.. .. ..	.. .. ..	.. .. ..	.. .. D	.. .. ..
21	.. .. ..	.. .. ..	.. .. D	.. .. D	.. .. D	A .. ..
23	.. .. ..	.. .. ..	.. .. ..	.. .. D	.. .. D	.. P ..
24	.. .. ..	.. .. ..	.. .. ..	A .. D	A .. D	.. .. ..
25	A .. D	.. .. ..	A .. D	.. P ..	.. .. ..	.. .. ..
26	.. .. ..	.. .. ..	A .. D	A .. D	.. .. ..	.. .. ..
Appeared	2	2	2	3	3	4
Persisted	3	2	0	3	3	3
Disappeared	1	0	3	6	7	2

reflection of carditis. Joint pain might be relieved, and precordial pain and tenderness, although due to carditis uninfluenced in its course, were often lessened through the analgesic effect (table 2). Occasionally, serous pericarditis and pleurisy were apparently hastened to their resorption through the anti-exudative action of the drug. Joint exudates responded in the same way, but this effect was often more slowly manifest than the relief from pain and tenderness.

5. The evolution of pathologic changes of a proliferative nature in the course of the disease was apparently uninfluenced by medication. The evidence indicated that carditis was not allayed. Gallop rhythm, precordial pain and tenderness and pericardial rub frequently appeared and persisted (table 2). Furthermore, changes in the electrocardiogram (e. g., prolonged conduction time, inverted T waves), persistently rapid pulse and the development of murmurs indicating progressive valvular

deformity, together with increasing volume of the heart, were all observed during the course of therapy. Other evidences of persisting inflammatory activity of a proliferative character were not abated. Table 2 indicates the appearance and persistence of nodules, rash and fibrinous pleurisy. In addition to these, the presence of leukocytosis and a downward trend of the weight curve, both valuable indexes of persisting infection, were often not modified by medication.

6. Two of the patients observed had chorea in addition to other rheumatic manifestations. No lessening of the choreic movements was observed with full therapeutic doses of the drug.

7. Tonsillectomy and adenoidectomy were performed in ten instances when the patients were in relatively active stages of rheumatic fever. With therapeutic doses for a few days before and after the operation, relapses, which otherwise probably would have been provoked, did not occur.

One case was encountered in which the symptoms were not adequately relieved by amidopyrine (case 24, table 1). The dose was raised to 1.8 Gm. daily. This kept the temperature below 102 F., and it fell almost to normal after a week. Meanwhile, moderate inflammation persisted in the joints. Other drugs were not tried, because the patient was severely ill with carditis, and on previous admission it had been found impossible to secure any degree of comfort whatever in this patient with neocinchophen or sodium salicylate, for dosage was restricted by toxic manifestations.

In several instances (chart 3), the action of another drug was compared with that of amidopyrine. The latter, of course, was effective in much smaller doses. A ratio of 1:6 would roughly express the dose of amidopyrine equivalent to that of sodium salicylate or neocinchophen.

The effectiveness of small doses is not so important, however, as the feasibility of giving full, effective, therapeutic doses without limitations imposed by symptoms of toxicity. This is illustrated by case "O'B." represented in chart 3. The vomiting and abdominal pain provoked by neocinchophen in doses of 10 Gm. per day, which were given on the first two days of medication, and which, if continued, might have proved effective, forced reduction to 5 Gm. of sodium salicylate daily. This dose over a period of two weeks did not completely control fever or arthritis. Of more importance were the severe symptoms of toxicity provoked at the end of that interval. On discontinuing the drug for a few days, the temperature rapidly rose to 105 F.; then, 0.9 Gm. of amidopyrine in the course of one day reduced it to below 100 F. Following this, daily doses of 1.2 Gm., shortly reduced to 0.9 Gm., afforded complete relief without giving rise to any toxic symptoms.

Of greatest importance in our experience was the complete absence of side actions and the wide margin between effective therapeutic and

the probable toxic dose. These features rendered the drug particularly valuable in the treatment of patients in whom cardiac decompensation had developed during cycles of rheumatic activity. The entire absence of gastric irritation from amidopyrine permits the identification with certainty of the earliest symptoms of cardiac insufficiency arising from visceral congestion, such as epigastric discomfort and tenderness, nausea and loss of appetite. Furthermore, in the course of combined digitalis and amidopyrine therapy, the degree of digitalization may be controlled with increased certainty, because one is confident that the gastric symptoms provoked are due to the former drug.

The usual single dose given was 0.3 Gm. The largest daily dose was 2.4 Gm. In such relatively small amounts, the drug showed all the therapeutic effects to be expected from medication of this type, while no evidence of toxicity was manifest in any patient. One patient received 0.9 Gm. daily for six months; another 1.5 Gm. daily for one month, and another 1.2 Gm. daily for one and a half months. No gastro-intestinal disturbance, such as anorexia, abdominal pain, vomiting, diarrhea or constipation, could be attributed to it. There were no subjective sensations of dizziness, tinnitus or feeling of fulness in the head. No indications of kidney damage or altered renal secretory function were observed on weekly examinations of the urine. With full doses, a slight atypical reduction of Benedict's solution regularly occurred. In only one instance did the urine become pink on standing, presumably due to the formation of rubizonic acid.

SUMMARY AND CONCLUSIONS

Amidopyrine has been used widely as an effective antipyretic and analgesic in a variety of diseases. Excepting the results in typhoid fever, experience indicates that it may be employed in daily doses of at least 3 Gm. without provoking symptoms of toxicity. Instances of idiosyncrasy are less frequent than with many other drugs of this type.

In rheumatic fever, it has been found effective in patients not relieved by other drugs or unable to tolerate them in therapeutic doses; and total daily doses of less than 2 Gm. have been found adequate in this disease. The feasibility of giving effective quantities without provoking untoward side actions, as well as the wide margin between therapeutic and toxic doses, renders this drug particularly valuable in the treatment of patients with rheumatic fever.

PIGMENT METABOLISM AND DESTRUCTION OF BLOOD IN ADDISON'S (PERNICIOUS) ANEMIA *

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Since the employment of the liver treatment for pernicious anemia,[1] defective formation rather than increased destruction of blood has been emphasized by Minot and Murphy,[2] Peabody [3] and others as the primary factor in causing the anemia. The chief evidence in support of this view is that the ingestion of adequate amounts of liver is followed in a few days by a sharp rise and fall in reticulocytes, and in a few months by a restoration of the blood picture to normal. Relatively little attention has been given, however, to the fact that within the same time all signs of increased blood destruction also disappear.

Although it has long been known that the excretion of urobilinogen in pernicious anemia is high, no quantitative studies have been reported of the change in the amount of urobilinogen in the feces and urine which follows liver therapy. The results of such a study, complemented by corresponding hematologic observations, are described here. The significance of the observations on pigment metabolism in Addison's "pernicious" anemia is discussed.[4]

The most striking changes following treatment were observed in patients with pernicious anemia in a state of relapse. In these patients the excretion of urobilinogen was found to be many times the normal amount. This excessive excretion was nearly always associated with a serum bilirubin value that was higher than normal, and frequently, but not always, with appreciable amounts of urobilin in the urine. During the reticulocyte crisis induced by the ingestion of adequate amounts of

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1. Minot, G. R., and Murphy, W. P.: Treatment of Pernicious Anemia by a Special Diet, J. A. M. A. **87**:470 (Aug. 14) 1926.

2. Minot, G. R., and Murphy, W. P.: A Diet Rich in Liver in the Treatment of Pernicious Anemia: Study of 105 Cases, J. A. M. A. **89**:759 (Sept. 3) 1927.

3. Peabody, F. W.: The Pathology of the Bone Marrow in Pernicious Anemia, Am. J. Path. **3**:179, 1927.

4. A preliminary report of this work was published in the Proceedings of the American Society for Clinical Investigation, J. Clin. Investigation **7**:510, 1929.

liver, the excretion of urobilinogen fell sharply to within normal limits and remained at a normal level as long as this treatment was continued. At the time of the reticulocyte crisis, also, the serum bilirubin fell to a normal value, and urobilin ceased to be present in the urine in detectable amounts.

In cases of pernicious anemia with little anemia the excretion of urobilinogen was definitely increased, but it was not as high as in severe cases. Usually there was but little increase in serum bilirubin, and urobilin [5] was not demonstrable in the urine. Liver therapy in such patients evoked a low reticulocyte response with subsequent disappearance of the macrocytosis and a decrease in the excretion of urobilinogen to normal.

These observations support the following interpretation of the excessive pigment metabolism and of the effect of treatment: The abnormal red blood cells, showing great variation in size and shape with marked microcytosis and poikilocytosis as well as macrocytosis, characteristic of pernicious anemia in the state of relapse, are rapidly destroyed. There is, accordingly, an excessive excretion of urobilinogen associated with hyperbilirubinemia and sometimes with urobilin in the urine.[5] In the cases showing little anemia there is general macrocytosis but less variation in the size and shape of the red cells. These more uniform large cells have a longer life than the irregular forms present in relapse, but a definitely shorter life than that of normal red blood cells. There is, therefore, only a moderate increase in the excretion of urobilinogen with little change in serum bilirubin and usually no urobilinuria.[5] In both types of cases following liver therapy the bone marrow produces and supplies to the blood stream cells which become progressively more normal and which are less rapidly destroyed. According to this view, the primary factor in the excessive pigment metabolism is an abnormality of the red blood cells, one of the consequences of which is that they are more rapidly destroyed.

METHODS

The urobilinogen was estimated by the method of Terwen,[6] except in some of the earlier work, in which a band extinction method was employed. The values given in the tables are those for the stools only.

5. Throughout the paper the term "urobilinogen" is used in referring to the pigment in the stools and "urobilin" for the pigment in the urine. The pigment in the stools was measured as urobilinogen and the urine was tested for urobilin, any urobilinogen present being first oxidized to urobilin. The tests used for urobilin are not sufficiently delicate to detect the small amounts present in normal urine. Hence, it is frequently stated that no urobilin was found in the urine.

6. Terwen, A. J. L.: New Method for Quantitative Determination of Urobilin in Urine and Faeces: Preparation and Properties of Pure Urobilin, Arch. f. klin. Med. **149**:72, 1925.

as the amount excreted in the urine, even in cases with marked urobilinuria, was seldom as great as 5 per cent of that found in the stool. The presence of urobilin in the urine was detected by the copper sulphate chloroform and zinc acetate methods. Serum bilirubin was estimated by the Thannhauser and Anderson modification of van den Bergh's method as described by McNee and Keefer.[7] Results are expressed in van den Bergh units. Hemoglobin was measured in a Sahli hemoglobinometer corrected for the standard of Haden.[8] The percentage of reticulocytes was obtained by counting the number of reticulocytes among 1,000 red blood cells distributed in various parts of a smear that had been vitally stained with brilliant cresyl blue.

Urobilinogen in Feces: Zinc Acetate Method (Band Extinction Method).—The method employed for the determination of urobilinogen in the stools by the band extinction method was essentially that of Elman and McMaster.[9] The specimen of stool was made up to 1,000 cc. with water. A 25 cc. aliquot was shaken violently in a mechanical shaker for one hour with 75 cc. of acid alcohol (1,600 cc. of 95 per cent methylated alcohol and 25 cc. of concentrated hydrochloric acid made up to 2,500 cc. with distilled water). After shaking for one hour, there were added to 25 cc. of the mixture 1 Gm. of solid zinc acetate and 25 cc. of a saturated solution of zinc acetate in 95 per cent methylated alcohol. The mixture was shaken violently for a few moments and filtered. To the clear filtrate a few drops of tincture of iodine were added to convert the remaining urobilinogen to urobilin. It was not found necessary to leave the mixture of stool and acid alcohol standing overnight in order to permit the oxidation of the urobilinogen to urobilin. The same results were obtained whether the determination of the urobilin was carried out immediately after extraction or twenty-four hours later.

The determination of the urobilin content consisted of the dilution of the filtrate containing tincture of iodine and already diluted with an equal volume of a solution of saturated zinc acetate, with a standard diluting solution until the characteristic band of urobilin was no longer visible when the solution contained in a 15 mm. test tube was viewed with the slit of the spectroscope so adjusted that the strongest Frauenhofer lines of the solar spectrum were just visible. The standard diluting solution was also that of Elman and McMaster, consisting of 2,000 cc. of 60 per cent alcohol, containing 50 Gm. of zinc acetate and 2 cc. of concentrated hydrochloric acid filtered repeatedly until perfectly clear. The amount of urobilin present in the specimen is expressed by the dilution required for the extinction of the band. It was found that this dilution value, by coincidence, corresponded roughly with the excretion of urobilinogen expressed in milligrams as determined by the method and standard of Terwen. This was true especially for the higher concentrations of urobilinogen in the stool.

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7. McNee, J. W., and Keefer, C. S.: The Clinical Value of the van den Bergh Reaction for Bilirubin in Blood, Brit. M. J. **2**:52, 1925.

8. Haden, R. L.: The Normal Hemoglobin Standard, J. A. M. A. **79**:1496 (Oct. 28) 1922.

9. Elman, R., and McMaster, P. D.: Studies on Urobilin Physiology and Pathology: I. The Quantitative Determination of Urobilin, J. Exper. Med. **41**: 503, 1925.

Urobilinogen in Feces: Terwen's Method.[6]—Most of the estimations of urobilinogen excreted in the feces were made with the method of Terwen. At first the daily specimens, later the specimens for three days, were thoroughly mixed and a 5 Gm. aliquot, or more, depending on the concentration of urobilin in the stool, was weighed out on paraffined filter papers. The stool was scraped off the filter paper, ground up in a mortar with distilled air-free water and made up to 50 cc. Fifty cubic centimeters of a 16 per cent solution of ferrous ammonium sulphate was added and then, with continuous stirring, 50 cc. of 12 per cent sodium hydroxide. The mixture was transferred to a flask, stoppered so that all air was excluded, and set away in a dark room overnight at room temperature.

At the end of this period the mixture was filtered through a folded filter paper. Two cubic centimeters of the filtrate was transferred to a small separating funnel; from 0.5 to 1 cc. of a 20 per cent solution of tartaric acid (to acidify the solution) and 20 cc. of ether (which previously had been washed with 30 per cent sodium hydroxide and four times with air-free distilled water) were added. The mixture was shaken violently, approximately sixty times, in the stoppered separatory funnel. Ten cubic centimeters of the supernatant ethereal solution was measured into a second separatory funnel, and a knife point of Ehrlich's aldehyde and 10 drops of concentrated hydrochloric acid were added. This mixture was shaken for exactly one and a half minutes; a small amount of air-free distilled water was added and finally enough saturated sodium acetate, usually 2 cc., to render the solution no longer acid to congo red. After a short period of further violent shaking, the colored compound of urobilinogen with Ehrlich's aldehyde was dissolved in the lower aqueous solution. This was run off. To the remaining supernatant ethereal solution 5 drops of concentrated hydrochloric acid was added and the solution again shaken for one and a half minutes; 1 cc. of a saturated sodium acetate solution was added with a little more water; the mixture was again shaken and the colored aqueous solution again run off. This was repeated until there was no significant amount of color in the aqueous solution.

The different fractions of colored solution were joined and diluted until the intensity of color was approximately equal to that of the standard solution. The standard color solution consisted of 1.0 cc. of a 0.05 per cent solution of phenolphthalein in absolute alcohol and 5 cc. of saturated sodium carbonate (at room temperature) diluted to 100 cc. The unknown was compared with the standard in the colorimeter. According to Terwen, the intensity of color in the standard solution is equivalent to that of a solution of 0.4 mg. of urobilinogen per hundred cubic centimeters. From this value, the total weight, dilution and colorimetric readings were converted to the number of milligrams excreted.

Urobilin in Urine.—In the urine, any urobilinogen present was first oxidized to urobilin and its presence as such determined by either the copper sulphate-chloroform or the zinc acetate method; the former method has been used as a routine test in the Toronto General hospital for a number of years since its introduction by Dr. F. W. Rolph. Ten cubic centimeters of urine is acidified with a few drops of 10 per cent acetic acid, and 1 cc. of 20 per cent copper sulphate is added to oxidize any urobilinogen present to urobilin. Two cubic centimeters of chloroform is introduced and the tube is allowed to stand overnight. The urobilin passes into the chloroform layer, coloring it yellowish to pink, depending on the acidity. The characteristic band is seen in the spectrum. The zinc acetate method was frequently used in addition. The two tests are about equally sensitive and neither gives a positive reading with normal urine.

METHODS AND TREATMENT USED IN THE WARD

The stools were collected daily and kept in covered cardboard boxes. At first the determinations of urobilinogen were made every day. Later it was found that the value for the mixed stools of three consecutive days was essentially the same as the sum of the three separate determinations. From this time on the stools were mixed in three day periods. In order to secure stools as regularly as possible frequent small doses of cascara were given when necessary. In some cases of combined degeneration of the spinal cord it was especially difficult to obtain daily specimens even with the employment of cathartics. In such circumstances, when there was no stool on a given day, a small saline enema was administered the following morning. In spite of these precautions, there was considerable variation in the weight and urobilin content of the grouped three day stools of these patients.

In nearly all the cases reported here the daily intake of fat, carbohydrate and protein was kept constant throughout the period of observation, and in some cases the same articles of food were given each day. Toward the end of this study when it had become clear that the diet was not an important factor in the excretion of urobilinogen, greater variety was allowed.

After periods of observation of varying length, depending on the patient's condition, some form of liver therapy was administered. One patient received the Eli Lilly extract derived from 300 Gm. of whole liver; some were given cooked whole liver in amounts varying from 100 to 300 Gm. daily, and others were given the juice expressed under pressure from minced whole liver that had been steamed for one-half hour. The latter preparation, which has been in common use in this hospital, is easily taken, and when the juice from 300 to 600 Gm. is given daily, a good reticulocyte response is induced. In two cases, a period in which ineffective extracts were given preceded adequate liver therapy. In most instances dilute hydrochloric acid was not prescribed.

The urobilinogen excretion of a number of normal young physicians and several patients with chronic neurologic disease was also determined. Of the latter group none had any symptoms or signs of disease of the liver or blood-forming organs, and all were in a state of good nutrition and good general health. One of them received a high fat, low carbohydrate diet; another was given in four successive periods, each of from ten to fourteen days' duration, the ordinary ward diet and diets high in carbohydrate, protein and fat, respectively. The results showed clearly that even these radical changes in diet did not alter the amount of urobilinogen excreted.

In order to observe the changes in pigment metabolism in conditions in which increased destruction of blood is known to occur, the excretion of urobilinogen was followed in a case of polycythemia vera treated

vigorously with phenylhydrazine and in a case of dementia paralytica treated with malaria. Concomitant observations of serum bilirubin, red blood cells, white blood cells and hemoglobin were made before, during and after treatment.

REPORT OF CASES

Cases of Pernicious Anemia in Relapse.—CASE 1.—M. G., the patient, aged 59, had a typical case of pernicious anemia and had been ill for four or five years. On admission in his third severe relapse he was weak and

TABLE 1.—*Results of Liver Therapy in Case 1**

Date	Hemoglobin, per Cent	Red Blood Cells, Millions	Reticulocytes, per Cent of Red Blood Cells	Serum Bilirubin, van den Bergh Units	Urobilinogen in Feces, Mg. Daily	Urobilin in Urine
June, 1929						
9	24	1.0	...	2.9	...	0
17	..	...	...	3.4	340	0
18	23	0.8	1.6	...	340	0
19	..	...	...	...	340	0
20	..	...	...	2.2	444	0
21	..	...	...	...	444	0
22	..	...	1.2	...	444	0
23	..	...	1.7	...	196	0
Liver begun						
24	..	...	...	3.0	196	0
25	..	...	...	...	196	0
26	..	...	...	...	428	0
27	..	...	...	2.6	428	0
28	..	...	...	...	428	0
29	..	...	9.2	...	296	0
30	..	...	10.8	...	296	0
July, 1929						
1	42	...	10.4	...	80	0
2	53	2.8	6.2	1.3	80	0
3	..	...	...	...	80	0
4	..	...	3.4	1.0	148	0
5	..	...	3.0	...	148	0
6	54	2.6	2.3	...	148	0
7	..	...	2.1	...	132	0
8	..	...	...	1.5	132	0
9	..	...	...	...	132	0
10	56	2.2	1.2	...	60	0
11	64	2.7	...	...	60	0
12	..	...	...	...	60	0
13	..	...	...	...	56	0
14	..	...	...	...	56	0
15	67	2.8	0.5	0.6	56	0

* M. G., 67 Kg. in weight, with a severe case of pernicious anemia, was treated with 100 Gm. of whole liver daily, beginning on June 24, 1929.

pale and had a slight icteric tint. The hemoglobin content was 24 per cent, and the red blood cell count, 1,000,000; the blood smear showed the marked macrocytosis, microcytosis and poikilocytosis characteristic of the state of relapse. He was given daily the rather small dose of 100 Gm. of cooked whole liver, which nevertheless induced a definite reticulocyte response. Observations were begun one week before the administration of liver and were carried on during the first three weeks of this treatment. The results are shown in table 1 and chart 1.

The striking feature here, found also in other severe cases of pernicious anemia, is the sharp change in the excretion of urobilinogen. Initially there was a very great output of urobilinogen, which persisted after the beginning of liver therapy until the appearance of the reticulo-

cyte response. Beginning at about the peak of this response the excretion of urobilinogen fell sharply to normal within a few days. Initially the serum bilirubin was also increased and it, too, fell to normal during the reticulocyte crisis. It is noteworthy that this excessive excretion of urobilinogen in the stools and the definite increase in serum bilirubin were not accompanied by the excretion of demonstrable amounts of urobilin in the urine.

Case 2.—A. G., the patient, aged 59, had been treated in the hospital in 1928 during a former severe relapse. At that time, although the stools were collected irregularly, there was a tremendous excretion of urobilin associated with a definite increase in serum bilirubin, but demonstrable amounts of urobilin occurred

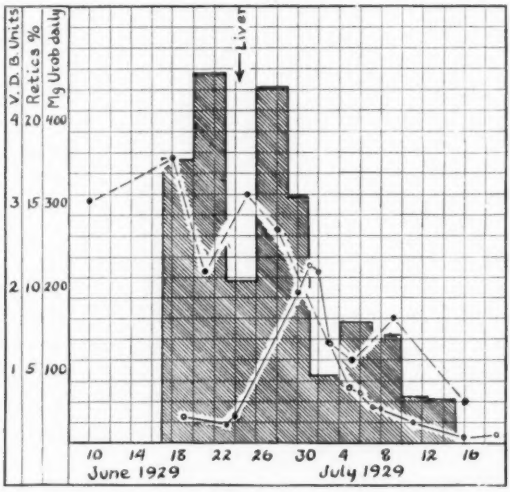

Chart 1.—Results in case of pernicious anemia in severe relapse (case 1, M. G., showing hemoglobin 24 per cent, red blood cells 1,000,000 and white blood cells 2,000). In this and the following charts, the broken line indicates the serum bilirubin in van den Bergh units; the solid line, percentage of reticulocytes, and the cross-hatched area, milligrams of urobilinogen in the stool daily.

in the urine only on rare occasions. He responded well to treatment and was discharged in April, 1928, with a hemoglobin content of 75 per cent, red blood cells numbering 3,600,000, a normal excretion of urobilinogen and a normal reaction of the serum to the van den Bergh test. He ceased to take liver a few days after his discharge, and he returned to the hospital in a severe relapse on Jan. 1, 1929. After a seven day observation period he was given, for fourteen days, a liver extract that proved to be ineffective. During this two weeks he became worse, although there was a slight increase in reticulocytes. The juice expressed from 800 Gm. of liver was then given daily. He responded well with a high percentage of reticulocytes and corresponding general improvement. The results are shown in table 2 and chart 2.

The excretion of urobilinogen and the serum bilirubin values before treatment were highest in this series. Toward the latter part of the reticulocyte response the serum bilirubin fell abruptly. Unfortunately the stools were lost for the few days just at the time that adequate liver

TABLE 2.—*Results of Liver Therapy in Case 2**

Date	Hemoglobin, per Cent	Red Blood Cells, Millions	Reticulocytes, per Cent of Red Blood Cells	Urobilinogen in Feces, Mg. Daily	Serum Bilirubin, van den Bergh Units	Urobilin in Urine	Nonprotein Nitrogen
January 2, 3, 4, 5	32	1.2	0.6	720	3.2	++ trace 0	..
6, 7, 8	..	...	...	312	5.6	0	45
9, 10, 11	33 30	1.5 1.2	0.3 0.7	588	3.6	trace	..
12, 13, 14, 15	26	1.2	0.3	480	4.0	0 trace	..
16, 17	..	...	1.1 1.2	Patient incontinent: some stools lost	3.8	++	57
18, 19, 20, 21	22	...	1.8 1.2 1.6		5.2	++ ++	66
22, 23, 24	21	...	1.1		6.0	+++	65
25, 26, 27	26 29	1.3	2.8 6.0		5.2	+++	40
28, 29, 30	35 40	1.6 2.1	39 40 23	72	4.0 4.8 2.6	++	40
31, February 1, 2	41 50	2.7	1.2 2.4	52	1.4	++ trace 0	..
February 3, 4, 5	..	...	1.2	248	0.8	0	..
6, 7, 8, 9	52	2.5	1.1	52	0.8	0	..
10, 11, 12, 13	54	3.9	0.6	32	1.0	0	..
Interval, 3 weeks							
March 5, 6, 7	62	...	...	24	0.6	0	..
8, 9	..	...	...	44	...	0	..
10, 11	..	...	...	36	0.6	0	..
12, 13, 14	64	4.3	...	64	...	0	..
15, 16	..	...	...	68	...	0	..

* A. G., 77 Kg. in weight, with pernicious anemia, was in severe relapse. From Jan. 8 to 21, 1929, he was given an ineffective extract. Beginning on January 22, he received the juice expressed from 800 Gm. of liver daily. The results are tabulated in periods, usually of three days each, during which all stools were mixed for urobilin determination. When any of the other values changed materially during a given period the daily values for that period are given in order from above downward in the appropriate column.

therapy was begun. The curves show, however, that the excretion of urobilinogen had decreased before the peak of the reticulocyte crisis. Ten days after the first administration of "liver juice" the urobilinogen excreted was about one-tenth its initial value, and this low level was maintained six weeks after the termination of the reticulocyte response.

In this case there was a striking increase in the amount of urobilin in the urine when the patient became worse during the administration of the ineffective extract. At the same time, the serum bilirubin increased; the blood nonprotein nitrogen rose from 45 to 65 mg. per hundred cubic centimeters, the bleeding time was prolonged and purpura appeared; the heart was dilated and the liver enlarged. The patient became extremely ill, stuporous and somewhat incontinent of urine and feces. Although

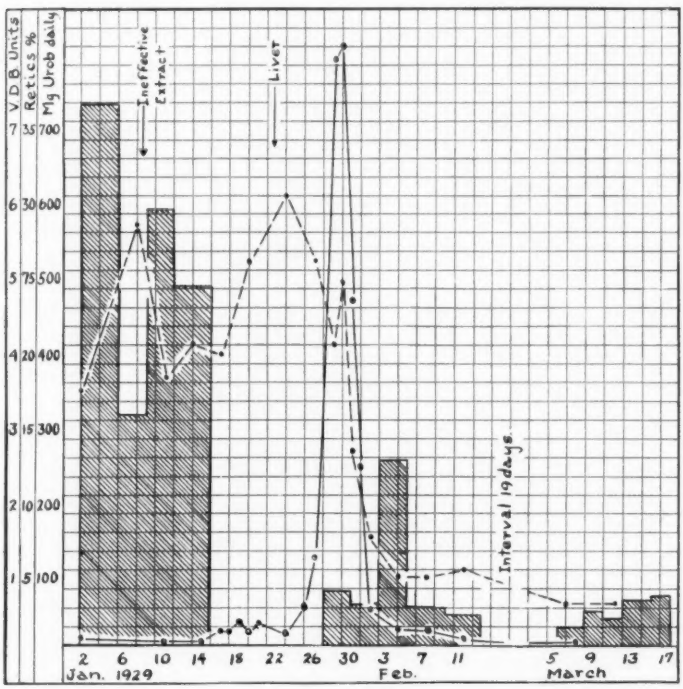

Chart 2.—Results in case of pernicious anemia in severe relapse, in which an ineffective extract and then adequate liver therapy were given (case 2, A. G., showing hemoglobin 32 per cent, red blood cells 1,200,000 and white blood cells 5,400).

many factors had changed, it is probable that the increased urobilinuria is to be attributed to the damage to the liver that occurred at this time. During the downward curve of the reticulocyte response the urobilinuria ceased and, at the same time, there was general improvement in the condition of the patient: his mental state cleared; he improved quickly in strength and sense of well being; the liver became normal in size; bleeding time decreased and purpura disappeared; the nonprotein nitrogen

and serum bilirubin values fell to normal and henceforth favorable progress continued.

CASE 3.—A. F., the patient, aged 82, had suffered from slowly increasing weakness and lack of energy for two or three years. In the last three months before her admission to the hospital, on Oct. 10, 1928, she became much worse. There were marked pallor, great weakness, generalized edema and drowsiness.

CASE 3.—*Results of Liver Therapy in Case 3* *

Date, 1928	Hemoglobin, per Cent	Red Blood Cells, Millions	Reticulocytes, per Cent of Red Blood Cells	Urobilinogen in Feces, Mg. Daily	Serum Bilirubin	Urobilin in Urine
October 11	18	0.9	...	...	...	.....
16	22	...	3.0	...	...	.....
18, 19, 20	25	1.0	...	204	2.2	trace
21, 22, 23	28	1.0	1.4	356	...	0
24, 25, 26	30	1.3	2.8 5.8	320	2.8	+ 0 0
27, 28, 29	34	1.5	3.8 6.3 9.5	284	...	0 + ++
30, 31, Nov. 1	32 35	1.3	4.5 6.6 4.5	236	3.2	++ ++ ++
November 2, 3, 4	43	1.9	4.4 8.2 15.9	108	0.8	++ + trace
5, 6, 7	40 48	1.8 2.0 2.4	17.0 19.2 9.6	160	0.6	trace 0 0
8, 9, 10	50 54	2.5	6.5 4.9 1.4	80	...	0
11, 12, 14	51	2.5	1.6 1.4 0.9 0.7	64	0.6	0
Interval, 10 weeks						
1929						
January 25, 26, 27	76	4.6	1.4	112	...	.....
28, 29, 30	..	...	...	112	...	.....
31, Feb. 1, 2, 3	70	4.2	1.2	76	...	.....

* A. F., aged 82 years, 40 Kg. in weight, had pernicious anemia. She was improving in a spontaneous remission when an acute otitis media developed, on Oct. 28, 1928. Beginning October 29, she was given daily an extract of 300 Gm. of liver. The results are tabulated in three day periods. When values changed daily the values for each day of a given period are given in order, from above downward, in the corresponding column; otherwise, just one figure is given for the three day period.

The hemoglobin content was 18 per cent, and the red blood cells numbered 900,000. She improved spontaneously and by the time liver treatment was given, the hemoglobin had risen to 34 per cent and the reticulocytes to 6.3 per cent of the red cells. At this time an acute otitis media developed and her condition became serious. She was given an extract of 300 Gm. of liver daily. After a few days there was a further sharp increase in reticulocytes to 19.2 per cent. The otitis media subsided following paracentesis and the patient improved rapidly. The results are summarized in table 3 and chart 3. This patient made an excellent recovery and now after more than one year on liver therapy she continues to feel well.

An interesting feature of this case is that, in spite of a definite spontaneous increase in reticulocytes and an increasing concentration of hemoglobin the excretion of urobilinogen was great and remained so until just before the reticulocytes rose to a much higher level following the administration of liver extract. During this induced reticulocyte crisis, the excretion of urobilinogen fell to normal.

The output of urobilinogen in this instance was, however, less than that in equally severe cases in which there was no spontaneous increase in reticulocytes and in which the hemoglobin was either stationary or falling. In this case, also, the urobilin in the urine definitely increased when the patient became quite ill with otitis media and disappeared at

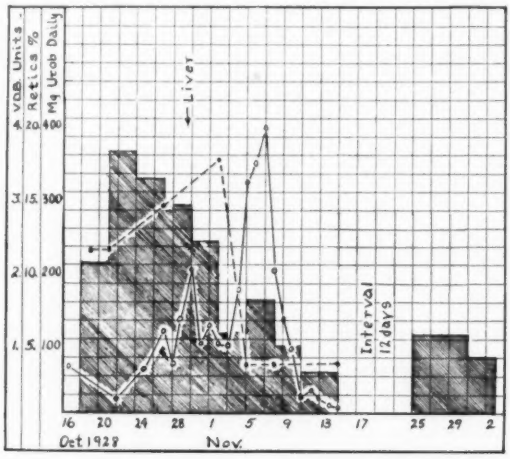

Chart 3.—Results in case of pernicious anemia in severe relapse in woman, aged 82, with spontaneous reticulocyte response (case 3, A. F., showing initially hemoglobin 18 per cent, red blood cells 900,000 and white blood cells 4,500).

the peak of the reticulocyte response. Three months after the beginning of liver treatment the output of urobilinogen was still within the normal limits.

In table 4 are presented values for the excretion of urobilinogen, van den Bergh test of the serum, reticulocyte percentage and red blood cell count in four other cases (cases 4, 5, 6 and 7) of severe pernicious anemia before and during the first few weeks of liver treatment. In all four cases there was an initial very great output of urobilinogen, which fell off sharply during the reticulocyte response. The serum bilirubin also reached normal levels during this period, and urobilinuria, when present, disappeared before the end of the crisis.

It is interesting to note the absence of parallelism between the values for fecal urobilinogen and serum bilirubin and the presence of urobilin in the urine. With a fecal urobilinogen output of 493 mg. daily, case 4 showed a slight increase in serum bilirubin, and a trace of urobilin in the urine on one occasion only. The initial serum bilirubin in G. M. (case 6),

TABLE 4.—*Summary of Results in Four Cases of Pernicious Anemia in Relapse* *

Day	Case 4 (C. J., Aged 62; Weight, 53 Kg.)†					Case 5 (W. C., Aged 46; Weight, 64 Kg.)‡					Case 6 (G. M., Aged 46; Weight, 60 Kg.)‖					Case 7 (G. D., Aged 53; Weight, 57 Kg.)#				
	Urobilinogen in Feces, Mg. Daily	Urine Urobilin	Serum Bilirubin	Red Blood Cells, Millions	Reticuloeytes, per Cent	Urobilinogen in Feces, Mg. Daily	Urine Urobilin	Serum Bilirubin	Red Blood Cells, Millions	Reticuloeytes, per Cent	Urobilinogen in Feces, Mg. Daily	Urine Urobilin	Serum Bilirubin	Red Blood Cells, Millions	Reticuloeytes, per Cent	Urobilinogen in Feces, Mg. Daily	Urine Urobilin	Serum Bilirubin	Red Blood Cells, Millions	Reticuloeytes, per Cent
Av.§	...	..	1.7	1.9	<0.3	376	+ to 0	1.7	1.2	<0.3	...	..	...	0.75	0.3	469	+	1.5	1.1	<0.2
1	...	..	...	...	...	440	0	...	...	<0.3	...	+	...	0.8	0.3	416	+	...	...	...
2	...	..	...	...	...	440	trace	...	1.7	0.15	396	++	2.2	...	...	636	+	...	1.1	<0.3
3	493	0	...	...	0.4	440	trace	...	...	...	216	+++	...	...	...	636	+	...	...	...
4	493	0	1.2	1.8	2.2	264	+	2.0	...	...	396	+++	...	0.8	7.4	636	++	...	...	0.9
5	493	0	...	2.1	2.2	264	0	...	...	...	180	+++	4.0	...	7.2	636	trace	...	...	0.3
6	341	0	...	2.0	2.0	264	0	...	1.7	3.5	180	++	...	1.0	25	360	+	...	1.0	0.3
7	341	0	...	2.1	13	132	0	...	...	...	180	+++	3.3	1.2	39	360	++	1.6	...	0.3
8	341	trace	0.7	2.9	11.6	132	0	...	...	5.0	176	+++	...	...	32	360	++	...	...	1.0
9	155	0	...	2.0	16	132	0	...	...	...	176	+	1.8	1.6	23	192	++	...	...	0.8
10	155	0	...	2.4	...	132	0	...	2.3	12	268	++	...	...	15	192	+	...	1.0	1.2
11	91	0	...	2.4	2.0	132	0	1.6	...	...	268	+	...	...	...	192	trace	1.4	...	0.9
12	91	0	...	2.6	2.2	132	0	...	...	...	56	++	1.2	...	5.2	176	+++	...	...	0.8
13	91	0	...	2.8	2.0	80	0	...	...	...	56	++	...	1.8	3.5	176	+++	...	1.0	1.8
14	91	0	...	...	...	80	0	0.6	2.5	10	56	+	...	...	...	176	++	...	...	2.8
15	112	0	...	2.9	0.8	68	0	...	...	...	56	+	...	2.1	...	232	++	...	...	2.8
16	112	0	...	...	1.4	68	0	...	...	...	168	+	0.8	...	...	232	++	...	...	16
17	112	0	...	3.3	...	68	0	...	...	2.5	168	trace	...	...	1.3	232	..	...	1.2	21
18	85	0	...	...	0.2	68	0	0.6	...	...	168	0	0.6	...	...	212	0	1.0	1.5	33
19	85	0	...	3.3	0.2	128	0	...	3.2	...	44	0	...	...	...	212	0	...	...	20
20	85	0	...	...	...	128	0	...	...	...	44	0	...	...	...	64	0	...	...	...
21	125	0	...	...	...	128	0	...	...	...	44	0	...	...	...	64	0	...	2.2	5
22	125	0	...	...	...	72	0	...	3.5	0.2	68	0	...	...	...	64	0	0.6	...	...
23	125	0	...	...	...	72	0	...	...	...	68	0	...	...	...	64	0	...	2.5	5.5
24	91	0	...	...	...	72	0	...	...	...	68	0	0.6	...	0.2	48	0	...	...	3.2
25	91	0	...	...	0.2	72	0	0.6	...	...	40	0	...	...	...	48	0	1.0	2.5	2.8
26	91	0	...	...	...	...	..	...	...	...	40	0	...	...	...	48	0	...	...	<1
27	78	0	...	...	...	...	..	...	...	...	40	0	...	3.6	0.1	52	0	...	...	...
28	78	0	...	...	...	...	..	...	...	...	84	0	...	...	...	52	0	...	...	...
29	78	0	...	...	...	...	..	...	...	...	84	0	...	...	...	52	0	...	...	1.0
30	42	0	...	...	...	...	..	...	...	...	84	0	0.6	...	...	...	..	...	...	...
31	42	0	...	...	...	...	..	...	...	...	32	0	...	...	...	...	..	...	...	...
32	38	0	...	4.5	<0.2	...	..	...	...	...	32	0	...	...	...	...	0	0.6	3.5	0.6

§ Average value in control period.

* The first line of figures gives the average value obtained before the beginning of liver therapy. In the second line are the values obtained for the first day on which liver was given, and succeeding lines in order are for succeeding days.

† This patient, a moderately severe case of pernicious anemia, was treated daily with Eli Lilly liver extract made from 300 Gm. of liver in June and July, 1927. In this case estimations of urobilin were made by the band method. All the others in this table were made by the Terwen method.

‡ This patient, in fairly severe relapse, was treated with the juice from 1,000 Gm. of liver daily in May, 1929, until the twelfth day; from then on he was given the juice of 600 Gm. of liver daily.

‖ This patient was in his second severe relapse, and was very ill. He was treated with juice from 1,500 Gm. of liver daily for the first eleven days, then juice from 1,000 Gm. daily.

This patient had a typical severe relapse. He was given first an inadequate extract for eleven days; then, from the twelfth day on, 300 Gm. of whole liver plus juice from 600 Gm. of liver daily. Showed rapid improvement.

who was seriously ill on admission and became much worse in the next few days, was 2.2 units. It rose to 4.0 units. His urine gave strong tests for urobilin. G. D. (case 7) with a very great fecal urobilinogen excretion also showed considerable amounts of urobilin in the urine, but his serum bilirubin did not rise at any time above 2 units. Like G. M., he was also seriously ill.

In a much larger series of cases than are reported here it has been common to find serum bilirubin values ranging from 2 to 4 units in patients with pernicious anemia in relapse. Large amounts of urobilin in the urine have been found only in those patients who were exceptionally ill, as in cases 2, 3, 6 and 7 of this series.

These cases of pernicious anemia in relapse show with striking regularity the rapid decrease in a high excretion of urobilinogen coincident with the latter part of the reticulocyte response. Beginning at about this time also the proportion of reticulated cells of normal size increases rapidly and the extremely large, as well as the very small and deformed cells in the smear become progressively fewer, so that by the time the reticulocytes have fallen to less than 2 per cent of the red blood cells the smear presents a much more normal appearance. In many instances also the color index at this stage has fallen to less than 1.

So rapid a disappearance of the grossly abnormal cells must, it seems, be due to actual destruction. There are no reasons for believing that they could be transformed so quickly into cells of nearly normal size and shape. On the other hand, the view that they have been destroyed is supported by the constant association of a high urobilinogen excretion with the presence of marked variation in the size and shape of the majority of the red blood cells, by the sharp drop in excretion of urobilinogen as the red blood cells rapidly become more normal in appearance, and by the persistence of a normal output while the hemoglobin and red blood cells increase and so long as normal values are maintained.

Cases of Pernicious Anemia with Little Anemia Frequently Presenting Symptoms and Signs of Subacute Combined Degeneration of the Spinal Cord.—A number of cases of pernicious anemia were observed at periods of the disease when the hemoglobin and red blood cells had not fallen to very low levels. Such patients frequently complained of symptoms of subacute combined degeneration of the cord, although a few suffered chiefly from increasing weakness before there was any well marked degree of anemia. The blood smear usually showed a general macrocytosis with few microcytes or poikilocytes. The blood picture, however, varied in degree from a condition of mild anemia and general fairly uniform macrocytosis to a state of moderate anemia with increasing microcytosis and poikilocytosis. The excretion of urobilinogen and, to some extent, the serum bilirubin also varied correspondingly. In none of this group was there any appreciable amount of urobilin in the urine.

Case 8.—H. S., the patient, aged 67, had been treated in the hospital in 1926 for pernicious anemia in severe relapse. Since discharge he had taken liver irregularly, never in adequate amounts. For some months before readmission on Oct. 26, 1928, he had suffered from weakness, lack of energy, and numbness and tingling of the hands and feet. His condition was relatively stationary during a

preliminary period of three weeks, his hemoglobin averaging 63 per cent. He was then given daily the juice expressed from 600 Gm. of liver. There followed a low reticulocyte response with definite clinical improvement and a gradual rise of the hemoglobin and red blood cells to normal. The results are presented in table 5 and chart 4.

The initial excretion of urobilinogen was definitely above the upper limit of normal; the serum bilirubin was normal, and there was no urobilin in the urine. During the reticulocyte response the urobilinogen output decreased somewhat, but after more than a month of liver therapy

TABLE 5.—*Results of Liver Therapy in Case 8* *

Date	Hemoglobin, per Cent	Red Blood Cells, Millions	Reticulocytes, per Cent of Red Blood Cells	Urobilinogen in Feces, Mg. Daily	Serum Bilirubin, van den Bergh Units	Urobilin in Urine
October 27	65	2.5	Rare	...	0.8	..
30, 31, Nov. 1	..	...	...	112	...	0
November 2, 3, 4	71	3.0	0.1	212	...	0
5, 6, 7	63	2.6	0.2	228	...	0
8, 9, 10	60	2.3	0.2	284	0.6	0
11, 12, 13	58	2.3	0.3	196	...	0
14, 15, 16	64	...	0.2	240	...	0
17, 18, 19	60	...	0.4	204	...	..
20, 21, 22	..	...	...	232	...	..
23, 24, 25	58	2.4	...	120	...	0
26, 27, 28	..	...	0.4	236	...	0
29, 30, Dec. 1	68	2.1	4.0	160	...	..
December 2, 3, 4	61	2.5	7.0	80	...	..
5, 6, 7	62	3.1	2.8	100	...	..
8, 9, 10	71	3.3	2.2	...	...	..
Interval, 7 days						
December 18, 19, 20	..	...	...	162	...	0
24, 25, 26	84	4.7	0.1	140	...	0
27, 28, 29	..	...	...	48	...	0
30, 31, Jan. 1, 2	..	...	...	144	...	0
Interval, 4½ months						
1929						
May 17, 18, 19	80	5.1	Rare	132	0.6	0
20, 21, 22	..	...	...	36	...	..
24, 25, 26	..	...	...	68	...	..
27, 28	..	...	...	80	0.5	0

* H. S., 54 Kg. in weight, had pernicious anemia with slight anemia; he was treated with the juice expressed from 600 Gm. of liver daily, beginning on Nov. 26, 1928.

it was still at a rather high level. A slight but definite macrocytosis persisted. Five months later, when the blood smear was normal, the excretion of urobilinogen had fallen to an average normal level.

In table 6 are presented data obtained from the three following cases of pernicious anemia with subacute combined degeneration of the spinal cord.

CASE 9.—H. D. had become unable to walk before the development of the anemia. On admission to the hospital his hemoglobin was 78 per cent, the red blood cells numbered 3,300,000 and the smear showed a well marked macrocytosis. He was obstinately constipated and the stools obtained with purgatives and enemas varied greatly in size. Before liver therapy the average daily output of urobilinogen in a twelve day control period was 195 mg. After a low reticulocyte

response the average for fifteen days was 114 mg. At the end of this time a slight anisocytosis persisted although the majority of the cells were normal in size. Later, when the blood smear was normal there was no opportunity to measure the excretion of urobilinogen.

Case 10.—J. W. was admitted with a complaint of difficulty in walking. He had been under liver therapy for over two years, during most of which time he was well. For many months, however, to save expense he had taken the extract of only one-third pound (151 Gm.) of liver daily. Even on this small dose he felt well until two months before admission, when stiffness and unsteadiness in walking began. His gait became progressively worse and he also suffered from some general weakness and lack of energy. On admission to the hospital his hemoglobin was 70 per cent and the red blood cell count, 2,700,000. The smear showed a definite anisocytosis with frequent large polychromatic cells, many normal-sized cells and some microcytes. Following the daily administration of

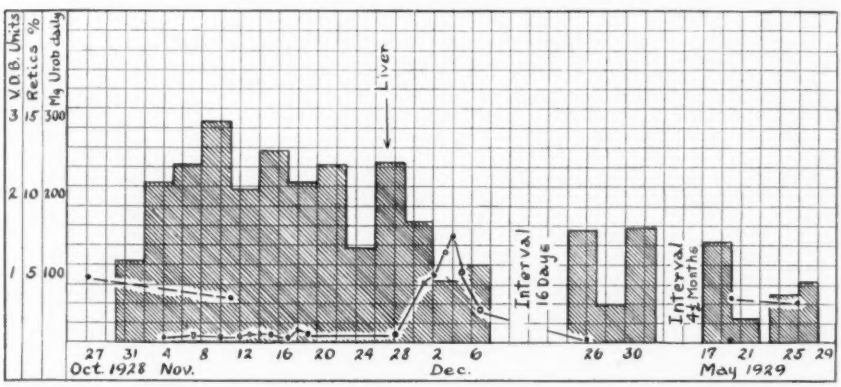

Chart 4.—Results in case of pernicious anemia (case 8, H. S., showing hemoglobin 65 per cent, red blood cells 2,500,000 and white blood cells 5,200).

the juice from 800 Gm. of liver, he improved greatly in general strength and sense of well-being; the reticulocytes fell to less than 0.5 per cent and the hemoglobin and red blood cells rose to normal. The excretion of urobilinogen could not be measured for more than two days before liver was given. An estimate of the quantity of urobilinogen excreted before treatment was obtained by averaging the output for these two days with that of the next four days, which gave the value of 244 mg. per day. Then followed a rapid decline to less than 100 mg. per day; at the same time the abnormal conformation of the red blood cells became much less marked.

Case 11.—On admission to the hospital, W. O. presented a typical picture of severe combined degeneration of the spinal cord with general weakness and lack of energy and a moderate degree of anemia. His hemoglobin was 59 per cent; the red blood cell count, 2,800,000. There was marked variation in the size and shape of the red cells with well marked macrocytosis and definite microcytosis, the blood picture of pernicious anemia in relapse. Following the daily ingestion

of the juice expressed from 600 Gm. of whole liver, the reticulocytes rose to a peak of 20 per cent on the eighth day, by which time most of the reticulocytes were of normal size. The urobilinogen of the feces, measured by the band method, fell from an initial level of almost 300 mg. daily to less than 75 mg. daily after

TABLE 6.—*Summary of Results in Three Cases of Pernicious Anemia with Subacute Combined Degeneration of the Cord and Mild or Moderate Anemia* *

	Case 9 (H. D., Aged 45; Weight, 59 Kg.)† Jan. 15 to Feb. 22, 1929					Case 10 (F. J. W., Aged 39; Weight, 76 Kg.)‡ March 13 to April 16, 1929					Case 11 (W. O., Aged 46; Weight, 52 Kg.)‖ Sept. 19 to Oct. 22, 1928				
Day	Urobilinogen in Feces, Mg. Daily	Urobilin in Urine	Serum Bilirubin	Red Blood Cells, Millions	Reticulocytes, per Cent	Urobilinogen in Feces, Mg. Daily	Urobilin in Urine	Serum Bilirubin	Red Blood Cells, Millions	Reticulocytes, per Cent	Urobilinogen in Feces, Mg. Daily	Urobilin in Urine	Serum Bilirubin	Red Blood Cells, Millions	Reticulocytes, per Cent
Av.§	195	0	0.6	3.3	...	...	0	1.8	3.2	1.9	278	trace	2.3	3.0	1.0
1	108	0	...	...	...	168	0	1.8	...	...	270	..	1.6	...	...
2	108	..	0.6	3.6	0.7	320	0	...	2.9	1.4	270	..	...	...	<1
3	108	..	...	...	0.3	320	0	...	...	...	...	..	...	...	...
4	216	..	...	...	0.5	320	0	1.6	3.3	1.5	240	..	1.2	...	<1
5	216	..	...	...	...	88	0	...	...	1.7	320	..	...	...	2.5
6	216	..	...	...	0.7	88	0	...	...	1.4	70	..	...	...	7.0
7	112	..	...	3.2	3.6	88	0	...	...	...	110	..	...	...	14
8	112	..	...	...	1.8	104	0	0.8	...	3.0	75	..	1.2	3.3	20
9	112	..	...	...	4.1	104	0	...	...	...	60	..	...	...	20
10	44	0	...	...	3.3	104	0	...	...	1.6	60	..	...	...	16
11	44	..	...	...	1.8	88	..	0.8	...	...	20	..	0.8	3.6	10
12	44	..	...	...	0.9	88	0	...	4.1	1.7	30	..	...	...	7.9
13	100	..	...	...	...	88	0	...	...	...	60	..	...	...	4.0
14	100	..	...	...	...	44	0	...	...	...	40	..	...	...	<1
15	100	..	...	3.8	...	44	..	1.0	...	...	30	..	0.6	...	<1
16	72	..	...	...	...	44	0	...	...	...	30	..	...	...	...
17	72	..	...	...	...	84	0	...	...	...	70	..	...	...	...
18	72	..	...	3.6	0.4	84	0	...	...	...	100	..	0.6	...	...
19	228	..	0.6	...	...	84	0	...	...	...	50	..	...	4.0	...
20	228	..	...	...	...	...	..	...	...	...	90	..	...	...	...
21	228	..	...	...	...	...	..	...	...	...	70	..	...	...	...
22	76	..	...	...	...	...	..	...	...	...	50	..	...	...	...
23	76	..	...	...	...	...	..	...	...	...	...	..	...	...	...
24	76	0	...	...	...	...	..	0.6	...	...	...	..	...	...	...
25	96	..	...	...	...	...	..	...	...	...	...	..	...	...	...
26	96	..	...	3.8	...	...	..	...	4.6	0.1	...	..	...	4.9	...
27	96	..	...	...	...	...	..	...	...	...	...	..	...	...	...
28	...	..	...	...	...	...	..	...	...	...	...	..	...	...	...
29	...	..	...	...	...	...	..	...	...	...	...	..	0.6	...	...
30	...	..	...	...	...	...	..	0.8	...	...	...	..	...	...	...
31	...	..	...	...	...	...	..	...	...	...	...	..	...	...	...
32	...	..	0.6	...	0.4	...	..	...	...	...	...	..	...	...	...

§ Average value in control period.

* As in table 4 the first line of figures gives the average value obtained before the beginning of liver therapy; in the second line are the values for the day on which liver was first given, and in subsequent lines, in order, the values for succeeding days.

† This patient had severe disease of the spinal cord and a little anemia. He was treated with 200 Gm. of whole liver daily. The red blood cell count rose somewhat slowly to 5,100,000 in two months.

‡ This patient had moderately severe disease of the spinal cord. Beginning March 18, 1929, he was given juice expressed from 800 Gm. of liver daily.

‖ This case showed severe combined degeneration of the spinal cord; the symptoms and blood picture were those of early relapse. Beginning Sept. 24, 1928, the patient received the juice expressed from 600 Gm. of liver daily. The urobilinogen determinations in this case were made by the band method, and the figures therefore represent only approximate values.

the reticulocyte response. Although the anemia in this case was not severe, the symptoms and blood picture were those of pernicious anemia in mild relapse. Associated with the greater abnormality in the appearance of the red blood cells, the excretion of urobilinogen was higher than in the two preceding cases. With

a good reticulocyte response the output of urobilinogen fell sharply to normal and, at the same time, the extreme macrocytosis and microcytosis disappeared.

A Case of Pernicious Anemia with Severe Anemia and Combined Degeneration of the Cord in Which the Response to Liver Therapy Was Unusually Slow.—CASE 12.—J. R., the patient, admitted to the hospital on April 13, 1929, had been treated in the hospital on previous occasions for pernicious anemia and chronic bronchitis with pulmonary emphysema. On his discharge in July, 1928, his hemoglobin was 91 per cent; he felt fairly well and was able to work. Since that time he had taken very little liver and after a few months he began to fail gradually in strength, weight, color and sense of well-being. He also suffered from unsteadiness and weakness, which grew worse until he became unable to

TABLE 7.—*Results of Liver Therapy in Case 12* *

Date, 1929	Hemoglobin, per Cent	Red Blood Cells, Millions	Reticulocytes, per Cent of Red Blood Cells	Serum Bilirubin, van den Bergh Units	Urobilinogen in Feces, Mg. Daily	Urobilin in Urine
April 13, 14	35	1.6	0.1	...	272	++
15, 16	40	1.4	...	1.6	292	++
17, 18, 19	30	1.0	...	1.2	5 days	++
20, 21	42	1.4	0.1	...	160	+
22, 23, 24	41	1.7	1.5	1.0	248	++
25, 26, 27, 28	39	1.6	2.0	1.4	64	+
29, 30, May 1, 2	38	1.3	3.2	1.0	88	++
May 3, 4, 5	..	...	May 5 5.0	...	152	+
6, 7, 8, 9	41	1.8	2.0	0.8	236	+
10, 11	..	...	0.8	...	104	trace
12, 13, 14	..	...	...	...	182	trace
15, 16, 17, 18	..	...	...	0.6	124	0
19, 20	..	...	...	0.6	28	0
21, 22, 23	57	2.7	Rare	...	5 days	0
24, 25	..	...	...	...	100	0
26, 27, 28	64	3.0	0.5	0.6	72	0
Interval, 3 months						
September 9, 10	90	4.9	†	...	56	0
11, 12	..	...	...	...	45	0
13, 14, 15	..	...	...	...	60	0
16, 17, 18	..	...	...	...	76	0
19, 20, 21, 22, 23	..	...	...	...	36	0

* J. R., weighing 61 Kg., had severe pernicious anemia with subacute combined degeneration of the cord. He received the juice from 800 Gm. of liver daily, beginning on April 20, 1929. The results are tabulated in periods during which stools were mixed for urobilinogen determinations. Representative values of other factors for each period are given.

† Occasional.

walk. He was admitted in a weak condition, presenting signs of advanced subacute combined degeneration of the cord. A summary of important laboratory observations is given in table 7 and chart 5.

His hemoglobin was 35 per cent; the red blood cells numbered 1,560,000, and the smear showed definite but not extreme macrocytosis, microcytosis and poikilocytosis. He was given daily the juice expressed from 800 Gm. of whole liver, but the response to such a large dose was small at first and very slow. The reticulocytes reached a peak of only 5 per cent on the fifteenth day and then gradually fell off. After eighteen days of treatment with liver there was still marked macrocytosis and microcytosis and as yet no appreciable increase in the hemoglobin percentage or red blood cell count. In the next few weeks, however, the anisocytosis became much less marked and the hemoglobin and red blood cells began to increase and from this time on the patient improved rapidly.

The response in this instance was similar to that in a case described by Minot, Murphy and Stetson.[10] Their patient showed no distinct reticulocyte response and little increase in the red blood cell count in the first six weeks of treatment, but after this period the red blood count rose rapidly to normal.

The initial urobilinogen output averaged 229 mg. daily, definitely a lower value than is usually found with such a degree of anemia in pernicious anemia. The patient was obstinately constipated, however, and the stools accordingly irregular in size. In spite of this irregularity it is clear that a high urobilinogen output persisted for over three weeks after the institution of liver treatment. As the character of the smear began to change and the hemoglobin and red blood count began to rise,

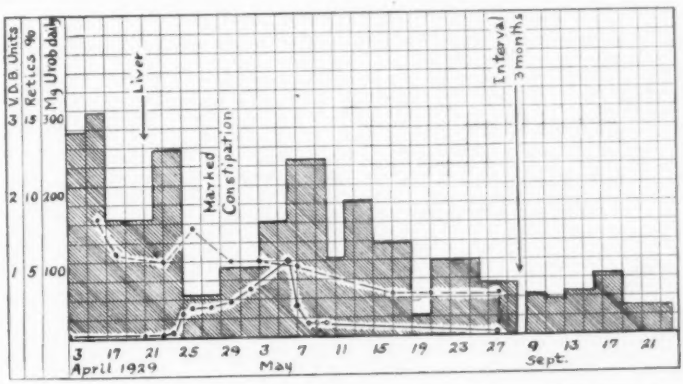

Chart 5.—Results in case of pernicious anemia in relapse, with extensive subacute combined degeneration of the cord (case 12, J. R., showing initially hemoglobin 35 per cent, red blood cells 1,600,000 and white blood cells 2,100). The hematologic response to liver therapy was slow and the excretion of urobilinogen remained at a high level for a corresponding period.

the excretion of urobilinogen fell to a definitely lower level. Three and one-half months later, when the smear was normal, the hemoglobin 90 per cent and the red blood cell count 4,900,000, the excretion of urobilinogen was well within normal limits.

This case clearly illustrates the relation of the high output of urobilinogen to the grossly abnormal red blood cells. In spite of the ingestion of large amounts of liver the response of the bone marrow was very slow and the smear retained the characteristics of pernicious

10. Minot, G. R.; Murphy, W. P., and Stetson, R. P.: The Response of the Reticulocytes to Liver Therapy, Particularly in Pernicious Anemia, Am. J. M. Sc. **175**:581, 1928.

anemia. As long as the marked anisocytosis persisted, the excretion of large amounts of urobilinogen continued. When the red blood cells became more normal in appearance in the third and fourth weeks, the output of urobilinogen fell off and the hemoglobin and red blood cell count rose. Later, when the red blood cells appeared normal, the excretion of urobilinogen was also normal. It may be noted that in this case

TABLE 8.—*Urobilinogen Content of the Stool in Five Physicians and Five Neurologic Patients on Various Diets**

Subject	Age	Weight, Kg.	Diet	Urobilinogen in Feces: Average per Day, Mg.	Day: 1	2	3	4	5	6	7	8	9	10	11	12	13
N. M. W. (normal)	28	65	House physician's†	34	28	28	28	16	16	52	52	52	..	..	..	..	..
E. J. M. (normal)	30	77	House physician's	50	60	60	64	64	8	8	68	68	..	..	..	..	..
R. F. F. (normal)	31	79	House physician's	24	32	32	24	24	16	16	16	..	..	..	..	..	..
K. E. F. (normal)	29	64	House physician's	52	12	12	12	108	108	56	56	56	56	..	..	..	..
T. A. C. (normal)	29	70	House physician's	129	68	68	68	180	180	156	156	156	..	..	..	..	..
J. W. (tabes dorsalis)	40	55	Ward diet	24	16	16	16	16	16	16	48	48	..	..	..	..	..
H. G. (muscular dystrophy)	19	60	Ward diet	24	24	24	24	20	20	20	28	28	28	..	..	..	..
H. C. (hemiparesis)	50	55	Ward diet	38	48	48	48	28	28	28	..	..	..	..	..	..	..
B. L. (epilepsy)	26	55	P. 40, F. 180, C. 40	48	60	60	60	36	36	36	48	48	48	..	..	..	..
			P. 40, F. 180, C. 20	64	24	24	76	76	76	80	80	80	..	..	..	..	..
L. B. (Friedreich's ataxia)	28	16	Ward diet	55	56	56	40	40	40	72	72	72	52	52	52	..	..
			P. 40, F. 50, C. 400	56	48	48	48	56	56	56	52	52	52	72	72	..	..
			P. 140, F. 160, C. 75	56	72	84	84	84	36	36	48	48	48	36	36	36	80
			200 Gm. of liver; high fat diet P. 40, F. 200, C. 80	56	80	80	48	48	48	48	48	48	..	..	..	..	..

* The days are numbered consecutively from the first day on which urobilinogen determinations were made. The stools were mixed usually in three day periods, occasionally in two or four day periods.

† Ordinary mixed diet.

urobilinuria persisted as long as the high excretion of urobilinogen in the feces continued.

EXCRETION OF UROBILINOGEN IN OTHER CONDITIONS

In order to appreciate the significance of the excretion of urobilinogen in cases of pernicious anemia, the urobilinogen of the stool was measured in a number of normal persons, in several patients with chronic neurologic diseases but good general health, in one case of polycythemia and in two patients with dementia paralytica in whom malaria was produced for therapeutic purposes.

Normal Excretion of Urobilinogen.—The values for excretion of urobilinogen of five healthy physicians and five neurologic patients are given in table 8. All ten persons had a normal red blood cell count, a normal percentage of hemoglobin, and normal serum bilirubin (less than 1 unit). None presented symptoms or signs of disease of the liver. None had urobilinuria.

The five physicians took the same ordinary mixed diet. One of them (T. A. C.) had an unusually large excretion of urobilinogen, averaging 128 mg. per day and amounting to more than twice that of any of the other controls. No reason for this variation was found. This value, however, lies within the normal range as described by Lichtenstein and Terwen.[11]

Of the neurologic patients, three were on ordinary ward diet. One was given a diet with a high fat and low carbohydrate content in treatment for epilepsy. The average daily output of urobilinogen in a seventeen day period was 56 mg., a figure well within the normal limit. The other, afflicted with Friedreich's ataxia and lying in bed all the time, was given in succession the ordinary ward diet for eleven days, a diet with a high carbohydrate content for eleven days; a diet with a high protein content, including 200 Gm. of whole liver, for thirteen days and a diet with a high fat content for eight days. The average daily excretion for these different periods varied only from 55 to 56 mg., thus showing that radical changes in diet did not affect the output of urobilinogen. It is of especial interest that the ingestion of 200 Gm. of whole liver daily by this patient failed to alter the excretion of urobilinogen.

The average daily output of urobilinogen of the ten subjects varied from 24 to 128 mg. In patients with pernicious anemia such values were obtained at or soon after the termination of the reticulocyte response. In the cases studied, the average daily excretion for the last six days of observation was between 50 and 90 mg., and one patient who had been under treatment for two years excreted 36 mg. per day in a nine day period.

The variation in the excretion of urobilinogen from period to period in a given person was largely dependent on the size of the stool, but in different persons there was considerable variation in the ratio

$$\frac{\text{Weight of stool, Gm.}}{\text{Urobilinogen content, mg.}}$$

Induced Destruction of Blood and Excretion of Urobilinogen.—It was important to ascertain the effect of induced destruction of blood on the excretion of urobilinogen. An excellent opportunity was pro-

11. Lichtenstein, A., and Terwen, A. J. L.: Blood Molting and Excretion of Urobilin, Arch. f. klin. Med. **149**:102, 1925.

vided by a case of polycythemia vera observed before and during treatment with phenylhydrazine.

CASE 13.—S. H., aged 55, presented a typical picture of this condition. On his admission to the hospital, in June, 1927, the red blood cell count was 10,600,000 and the hemoglobin 126 per cent. After observation for one week he was given 0.2 Gm. of phenylhydrazine hydrochloride daily for fourteen days. During this time the urobilin content of the stools and urine, the serum bilirubin, the hemo-

TABLE 9.—*Observations in a Case of Polycythemia Vera During Treatment with Phenylhydrazine Hydrochloride* *

Date, 1927	Red Blood Cells, Millions	Hemoglobin, per Cent	White Blood Cells, Thousands	Serum Bilirubin, van den Bergh Units	Urobilin in Stool§	Urobilin in Urine	Corpuscle Volume	Phenylhydrazine, Gm.
June 23	....	...	....	...	106	0	..	...
24	....	...	....	...	106	0	..	...
25	....	...	....	...	106	0	..	...
26	10.6	126	....	...	106	0	73	...
29	11.4	130	....	...	75	0	72	...
30	13	125	14.8	...	75	0	..	0.2
July 1	....	...	....	...	75	0	..	0.2
2	11.9	...	27	...	304	0	..	0.2
3	....	...	....	...	304	0	..	0.2
4	9.5	115	13.4	...	304	0	..	0.2
5	8.9	110	13	...	283	0	..	0.2
6	9.2	102	10	0.8	283	0	70	0.2
7	9.8	105	12.6	...	283	0	..	0.2
8	8.6	102	20.6	...	253	0	..	0.2
9	9.4	106	18.4	6.0†	253‡	0	64	0.2
10	....	...	....	...	253‡	0	..	0.2
11	7.6	96	13	...	Lost	0	..	0.2
12	7.9	92	23.8	7.5†	513	0	..	0.2
13	6.2	85	33.6	...	513	0	..	...
14	6.7	70	35.4	8.0	513	..	49	...
19	3.8	50	27.6	4.0	...	..	..	...
22	2.5	34	27	...	....	..	23	...
25	2.4	32	22.7	0.8	....	..	..	...
28	....	...	....	0.6	....	..	..	...
30	3.7	47	16	...	...	..	..	...
August 1	....	...	....	...	19	..	..	...
2	....	...	....	...	19	..	..	...
3	....	...	....	...	19	..	..	...
4	....	...	....	...	22	..	..	...
5	....	...	....	...	22	..	..	...
6	....	...	....	...	22	..	..	...
7	....	...	....	...	22	..	..	...
8	4.8	70	15.6	0.6	...	..	..	...

* S. H. (case 13), 47 Kg. in weight and suffering from polycythemia vera, was treated with 0.2 Gm. of phenylhydrazine hydrochloride daily from June 30 to July 13.

† Serum free from hemolysis.

‡ Bands of hematoporphyrin seen on examination of filtrate from stool.

§ Band reading; equals approximate number of milligrams of urobilinogen daily.

globin and the number of red and white blood cells were followed. The urobilin was measured by the band method, and the figures given therefore, represent only approximately milligrams of urobilinogen. The details are given in table 9 and chart 6.

The initial excretion of urobilinogen was at a rather high normal level. Following the administration of daily doses of phenylhydrazine, there was an early decided fall in red blood cells and the percentage of hemoglobin, and a simultaneous and considerable increase in the uro-

bilinogen content of the stool. Later, when the effect of the phenylhydrazine was more pronounced and a few days before the administration of the drug was discontinued, the serum bilirubin rose rather sharply and the patient became jaundiced. By this time the output of urobilinogen had become very great.

Unfortunately, it was impossible to measure the output of urobilinogen for two weeks after the drug was discontinued. On the day

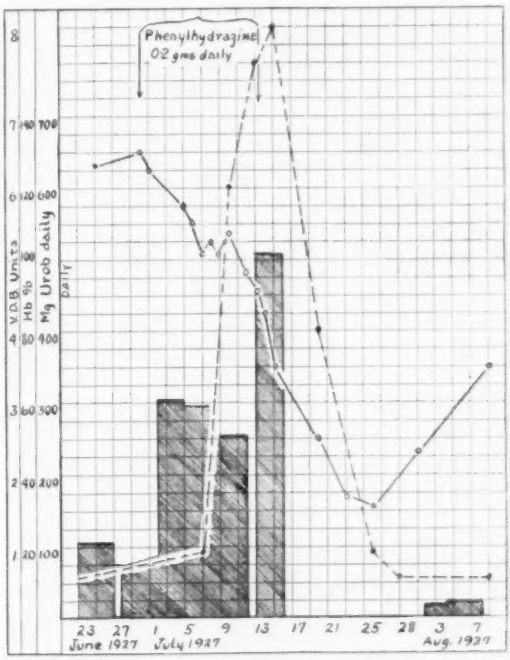

Chart 6.—Results in a case of polycythemia vera in which phenylhydrazine was given (case 13, S. H., showing initially hemoglobin 126 per cent, red blood cells 10,600,000 and white blood cells 14,800). The hematocrit reading was 73 per cent. In this chart the solid line indicates hemoglobin percentage; the broken line, as in the others, indicates serum bilirubin.

of the last dose the red blood cell count was 6,200,000 and the hemoglobin 85 per cent. Twelve days later the red blood count was 2,400,000 and the hemoglobin 32 per cent. By this time, however, jaundice had disappeared, the serum bilirubin was normal and it seemed that the effect of the phenylhydrazine was spent. Five days afterward, when estimations of urobilinogen were again undertaken, the hemoglobin and

red blood cell count were rising, serum bilirubin was normal and the excretion of urobilinogen was found to be much below its initial level. It is interesting that in the period before treatment and in the period of recovery there was some parallelism between the height of the red blood cell count and the level of excretion of urobilinogen. When the red blood cell count lay between 10,600,000 and 13,000,000, the output of urobilinogen averaged 92 mg. per day. In the period of recovery, with the red blood count between 3,700,000 and 4,800,000, the daily average was 21 mg. A similar relationship between the hemoglobin percentage and the excretion of urobilinogen in dogs was noted by McMaster, Broun and Rous.[12] Under the destroying influence of phenylhydrazine, the urobilinogen of the stool rose to at least 513 mg. per day, an output fully as great as the excretion in cases of pernicious anemia in severe relapse. With the greatly increased blood destruction the patient became jaundiced and the van den Bergh reaction of the serum rose to 8.0 units. As was to be expected in jaundice due only to increased destruction of blood, the direct reaction was negative. It is noteworthy also that, in spite of a greatly increased blood destruction, urobilin was present in the urine in amounts insufficient to give a positive test by the zinc acetate or copper sulphate-chloroform methods.

Excretion of Urobilinogen in Malaria.—In patients suffering from malaria with regular chills, it is usually considered that there is increased blood destruction.

CASE 14.—A. D., a man, aged 35, with dementia paralytica was admitted to the Toronto General Hospital in December, 1928, for malaria therapy. Although he was not robust in appearance there was no evidence of any other disease. In the control and incubation period the excretion of urobilinogen averaged 123 mg. per day, a rather high level. When the fever rose and regular chills occurred, there was a prompt increase in the urobilinogen of the stool, which reached a maximum of 429 mg. daily in a subsequent three day period. The serum bilirubin rose slightly. He became quite ill. The spleen and liver were enlarged and an appreciable amount of urobilin was found in the urine. The hemoglobin fell from 90 to 95 per cent to 78 per cent. The chills ceased spontaneously, the urobilinogen of the stool fell to a lower level, the serum bilirubin became normal, the urobilinuria ceased, the spleen and liver became smaller and the patient improved generally. The results are shown in table 10.

During the period of regular chills, estimation of the urobilinogen of the feces every day showed clearly, in spite of considerable irregularity in the size of the stool, that a huge increase in the output of urobilinogen occurred following each chill. Sometimes a small stool after

12. McMaster, P. D.; Broun, G. O., and Rous, P.: Studies of the Total Bile: I. The Effects of Operation, Exercise, Hot Weather, Relief of Obstruction, Intercurrent Diseases, and Other Normal and Pathological Influences, J. Exper. Med. **37**:395, 1923.

the chill had a much greater urobilinogen content than a large stool on the next day. For instance, a 95 Gm. stool for the day of a chill contained 872 mg. of urobilinogen, while a 216 Gm. stool on the subsequent day contained 84 mg. Often the increase in the urobilin output appeared in the stool that was passed the morning after the day of the chill.

Another patient given malaria therapy showed similar results although it was impossible to collect stools satisfactorily.

COMMENT

Relation of Destruction of Blood to Excretion of Urobilinogen.—Although it appears that any increase in the destruction of the blood is

TABLE 10.—*Observations in a Case of Dementia Paralytica in Which Malaria Therapy Was Given* *

Date, 1928	Maximum Temperature of the Period	Hemoglobin, per Cent	Red Blood Cells, Millions	Urobilinogen in Feces, Mg. per Day	Urobilin in Urine	Serum Bilirubin	Quinine Therapy, Grains Daily
December 9, 10, 11, 12.....	98.8	91	...	130	0	0.6	0
13, 14, 15.....	98.6	95	5.0	79	0	...	0
16, 17, 18.....	98.6	102	...	104	0	...	0
19, 20, 21, 22, 23....	104.6	..	...	108	0	0.8	0
25, 26, 27, 28, 29....	105	88	5.3	253	+	1.0	0
30, 31, January 1..	103.4	..	...	319	+	1.0	0
1929							
January 2, 3, 4.....	104	78	...	429	trace	1.2	0
5, 6, 7, 8.....	102	77	4.5	200	trace	1.4	0
9, 10, 11.....	100.2	80	...	286	0	...	0
12, 13, 14.....	99	78	...	364	0	0.8	0
15, 16.....	98.6	..	...	220	0	...	30
17, 18, 19.....	99	..	...	148	0	...	15
20, 21, 22.....	98.6	..	...	156	0	0.6	15
23, 24, 25.....	98.6	..	...	216	0	...	15

* A. D. (case 14), weighing 68 Kg., was inoculated with malaria-infected blood on Dec. 17, 1928. The first chill occurred on December 21. Although the chills were dying off spontaneously, quinine therapy was begun on Jan. 15, 1929.

accompanied by an increased excretion of urobilinogen, it is improbable that all the hemoglobin destroyed can be accounted for as urobilinogen. In dogs, Broun, Rous and McMaster [13] found that under ordinary conditions only a fraction of the estimated amount of destroyed hemoglobin was excreted as bilirubin. When blood destruction was increased, however, not only was there a great increase in the output of bilirubin but also a greater proportion of the hemoglobin lost could be accounted for as bilirubin.

There are further reasons for doubting the existence of a precise quantitative relationship between hemoglobin destroyed and urobilinogen

13. Broun, G. O.; Rous, P., and McMaster, P. D.: The Relation Between Blood Destruction and the Output of Bile Pigment, J. Exper. Med. **37**:733, 1923

excreted. Urobilinogen is a product of bacterial action, and it would be surprising if all the bilirubin excreted into the intestinal tract was converted quantitatively into urobilinogen. Constipation [14] and other factors have been found to reduce the amount of urobilinogen in the stools. The most that can be claimed, therefore, at present, is that the urobilinogen excreted represents a large fraction of the hemoglobin destroyed.

However, McMaster and his associates [15] have shown that urobilinogen in the stools is formed only from bilirubin excreted into the bowel, and that the amount of bilirubin excreted, independent of changes in diet, varies with the rate of blood destruction.

The great increase in excretion of urobilinogen accompanying known increase in destruction of blood is illustrated in the case of polycythemia in which phenylhydrazine was given and in the case of dementia paralytica in which malaria therapy was used. That such an increase occurs in hemolytic icterus has long been recognized. On the other hand, we know of no condition characterized by an increased excretion of urobilinogen in which it can be shown that increased destruction of blood does not occur.

The Hemoglobin Equivalent of Urobilinogen Excreted: (a) Normal; (b) Pernicious Anemia.—The average daily excretion in our controls was lower than that found by Lichtenstein and Terwen.[11] Like them, we found great individual variation, but our average for ten cases is rather less than half the average value in their series of fifteen. The excretion of urobilinogen in pernicious anemia, however, was similar in both series, although one of their cases showed a greater output than any of ours.

(*a*) Assuming that the blood constitutes 5 per cent of the body weight, and that 4 Gm. of urobilinogen is produced from 92 Gm. of hemoglobin, Terwen [6] calculated that one-one hundred and fortieth of the hemoglobin content of the blood in normal persons is excreted as urobilinogen every day. Calculating the rate for our controls in the same way, the daily normal excretion of urobilinogen is equivalent to about one-three hundred and fortieth of the blood hemoglobin, the maximum being one-one hundred and sixty-eighth.

(*b*) In cases of pernicious anemia, on the other hand, the relationship is very different. Assuming for purposes of calculation that the blood volume has the same proportion to body weight as in the normal condition, one finds that in patients with anemia of increasing severity

14. Elman, R., and McMaster, P. D.: Studies on Urobilin Physiology and Pathology: II. Derivation of Urobilin, J. Exper. Med. **41**:513, 1925.

15. Rous, P.; Broun, G. O., and McMaster, P. D.: Studies on the Total Bile: II. The Relations of Carbohydrate to the Output of Bile Pigment, J. Exper. Med. **37**:421, 1923; footnote 13.

the hemoglobin equivalent of urobilinogen excreted each day becomes a larger and larger fraction of the calculated blood hemoglobin of the body until in patients in severe relapse it may amount to more than one tenth of this total. Immediately after the reticulocyte response the fraction becomes less than one-one hundredth, and thereafter remains within normal limits. This is shown by the data presented in table 11. The cases are arranged in order of severity of the anemia. These figures show that in pernicious anemia there is an inverse relationship between the rate of destruction of blood and the severity of the anemia, and that in all cases destruction of blood falls off markedly under treatment with liver.

TABLE 11.—*The Value for the Fraction, Hemoglobin Equivalent of Average Daily Urobilinogen Excretion: Calculated Total Blood Hemoglobin in Cases of Pernicious Anemia at Different Levels of Hemoglobin Percentage* *

	Before Liver Therapy		Immediately After Reticulocyte Crisis			Late Observations Made		
		Hemoglobin Equivalent of Urobilin Excreted Daily			Hemoglobin Equivalent of Urobilin Excreted Daily			Hemoglobin Equivalent of Urobilin Excreted Daily
Case	Hemoglobin, per Cent	Total Blood Hemoglobin	Days After Beginning Treatment	Hemoglobin, per Cent	Total Blood Hemoglobin	Months After Beginning Treatment	Hemoglobin, per Cent	Total Blood Hemoglobin
9 (H. D.)	78	1/80	13–27	80	1/143	.	..	.....
10 (J. W.)	70	1/74	11–19	86	1/290	.	..	.....
8 (H. S.)	62	1/55	23–37	84	1/121	6	80	1/200
12 (J. R.)	35	1/30	17–25	40	1/ 50	5	90	1/318
			25–39	60	1/133			
5 (W. C.)	30	1/17	15–25	60	1/141	.	..	.....
2 (A. G.)	30	1/14	10–23	54	1/160	2	64	1/343
3 (A. F.)	29	1/13	11–17	55	1/106	3	70	1/109
7 (G. D.)	25	1/10	10–18	44	1/156	.	..	.....
1 (M. G.)	24	1/ 9	14–21	67	1/174	.	..	.....

* Only those cases in which Terwen's method was used are included.

If pernicious anemia were primarily a hemolytic anemia, it might be expected that a considerable increase in the destruction of blood could be observed before there was any appreciable fall in the percentage of hemoglobin, and that the excretion of urobilinogen would be greatest when the hemolytic agent was acting on the largest number of red blood cells. It is found, instead, that the urobilinogen increases as the cells become more and more abnormal in appearance, and that usually it is greatest, absolutely and relatively, when the actual number of red blood cells is very low. When the hemoglobin is about 20 per cent. the excretion of urobilinogen is equivalent to one tenth or more of the calculated blood hemoglobin of the body.

Relation of the Number of Reticulocytes to the Increase in the Red Blood Cells.—Minot, Cohn, Murphy and Lawson [16] noted in cases showing a marked reticulocyte response that the increase in the red blood cells up to the time of the peak of the response was often approximately equal to the number of reticulocytes per cubic millimeter. In a subsequent paper [17] it was remarked that such a relationship might be expected to exist "in so far as there has been no destruction of red blood cells, no change in distribution of body fluids, no maturation of reticulocytes to adult red blood cells, and no entrance into the circulation of nonreticulated erythrocytes." We found a similar relationship between the increase in red blood cells and the number of reticulocytes at or before the peak of the crisis in cases showing a very high reticulocyte response. Another explanation which takes into account the concomitant changes in the rate of destruction of blood is, however, possible. Before the commencement of liver therapy, the hyperplastic bone marrow produces large numbers of grossly abnormal cells—megalocytes, macrocytes, microcytes—that are rapidly destroyed. Following the ingestion of liver, the bone marrow is stimulated to supply, in addition to these abnormal cells, increasing numbers of immature (reticulated) red blood cells which have a longer expectancy of life. Equilibrium between the formation and the destruction of blood is maintained for a short time by the continued discharge of the abnormal cells into the blood stream, and the red blood count rises in virtue of the number of reticulocytes supplied. With the change in the character of blood formation in the bone marrow under the influence of liver therapy, more mature red blood cells, not so readily destroyed, enter the circulation. The reticulocytes of the circulating blood become mature, thereby reducing the proportion of reticulocytes in the blood smear to a normal number. The excessive excretion of urobilinogen ceases, and thenceforth the red blood count and hemoglobin rise gradually to normal.

Plasma Bilirubin in Pernicious Anemia: Its Relation to the Excretion of Urobilinogen.—In most cases of pernicious anemia the plasma bilirubin is increased, but its actual level is by no means parallel either to the severity of the anemia or to the amount of urobilinogen excreted, although all three tend to vary in the same direction. In mild cases there is a considerable increase in the excretion of pigment without any significant rise in the bilirubin of the plasma. In severe cases the

16. Minot, G. R.; Cohn, E. J.; Murphy, W. P., and Lawson, H. A.: Treatment of Pernicious Anemia with Liver Extract: Effects upon the Production of Immature and Mature Red Blood Cells, Am. J. M. Sc. **175**:599, 1928.

17. Cohn, E. J.; Minot, G. R.; Alles, G. A., and Salter, W. T.: The Nature of the Material in Liver Effective in Pernicious Anaemia, J. Biol. Chem. **77**:325, 1928.

plasma bilirubin is always increased, but among several such patients excreting approximately equal amounts of urobilinogen there may be considerable variation in its level. The plasma bilirubin rises when the patient becomes worse and is usually highest in the patients that are critically ill. The highest value we have noted was 8.0 van den Bergh units in a patient just before his death (in 1925). In no case was a direct van den Bergh reaction observed.

The rapid decrease in plasma bilirubin shown in all cases during the reticulocyte response has been observed by Minot and Murphy [1] and others.

Urobilinuria in Pernicious Anemia.—It has already been mentioned that urobilin can rarely be demonstrated in the urine in mild cases of pernicious anemia, and that it does not always appear in the urine in severe cases, even when the plasma bilirubin is high and when large amounts of urobilinogen are excreted in the feces. It is common to find small amounts of urobilin in the urine of patients in relapse; but strongly positive tests have been found only for patients that were seriously ill. In some instances patients were under observation while they became much worse: in these the transition was observed from negative tests or only traces of urobilin to such amounts that a positive test was obtained even when the urine was greatly diluted. In some instances there was an increase in the urobilinuria immediately after the beginning of liver therapy. In all cases, however, urobilin ceased to be demonstrable in the urine before the end of the reticulocyte response. It is probable that the increased urobilinuria in very ill patients is due, in part at least, to an associated disturbance in hepatic function.

The Cause of the Anemia.—There have been many different opinions as to the cause of the anemia and the associated derangement of blood pigment metabolism in pernicious anemia, but for many years the dominant views have been (1) that it is primarily a disorder of blood formation, and (2) that it is due to hemolysis or increased blood destruction. Minot, Murphy and Stetson [10] stated that they held to the conception of Pepper (1875) and Cohnheim (1876) that it is a disorder in the formation of blood. They have found it difficult to conceive that the prompt improvement following on liver therapy can be attributed to the arrest of a hemolytic process. Yet, they stated: "that a dysfunction of haemoglobin metabolism, which may partly be due to abnormal red blood cell destruction is a feature of the disease." Whipple [18] considered that

18. Whipple, G. H.: Pigment Metabolism and Regeneration of Hemoglobin in the Body, Arch. Int. Med. **29**:711 (April) 1922; Experimental Anemias, Diet Factors and Related Pathologic Changes of Human Anemias, J. A. M. A. **91**:863 (Sept. 22) 1928.

the anemia of pernicious anemia is the result of a deficiency of stroma-building material or a disturbance of the stroma-building mechanism with an overproduction of pigment substances rather than an increased destruction of red blood cells. The tissues of the body, he contended, become saturated with pigment material produced in excess of the limited number of red blood cells, and this excess production leads to increased excretion of bilirubin and urobilin. Krumbhaar,[19] on the other hand, while of the opinion that pernicious anemia is not primarily a hemolytic anemia, did not question the existence of increased destruction of blood in this disease. The excessive pigment metabolism, he wrote, is more likely a sign of increased blood destruction than of "elimination of hypothetical materials designed for haemoglobin formation but unavailable in the haemoglobin saturated state of the few functioning erythrocytes."

Peabody [3] clearly demonstrated that the hyperplasia of the abnormal cells in unusual regions of the bone marrow disappears in the remission that results from liver therapy. The bone marrow, now apparently normal, once more supplies normal red blood cells to the circulating blood.

To us it seems most probable that the essential disorder in the anemia of Addison's "pernicious" anemia is one of formation of blood, but that there is a resultant secondary increase in its destruction. An abnormal bone marrow produces abnormal cells that are rapidly destroyed. With slight anemia and general macrocytosis, the excretion of urobilinogen is definitely but not markedly increased. In cases showing greater anisocytosis and more irregularity in form of the red cells, usually with moderate anemia, the output of the urobilinogen (i. e., destruction of blood) is greater. When the smear shows the characteristic picture of severe relapse, the excretion of urobilinogen is very great. Destruction of blood preponderates over its formation, and severe anemia results.

Following liver therapy, the bone marrow is stimulated to supply large numbers of immature but more normal red blood cells (reticulocytes) that have a long duration of life. The production of the grossly abnormal cells ceases, and with their disappearance from the blood stream the excretion of urobilinogen falls off sharply. Adult erythrocytes, more and more nearly normal in appearance, with a normal duration of life, are now supplied. All signs of increased destruction of blood disappear. The red blood cell count and hemoglobin percentage rise and become normal. While the blood picture remains normal, the rate at which destruction of blood occurs also remains normal.

19. Krumbhaar, E. B.: Thoughts on the Morbid Processes Active in Pernicious Anaemia, Am. J. M. Sc. **175**:523, 1928.

SUMMARY AND CONCLUSIONS

1. In patients with Addison's "pernicious" anemia in a state of relapse the excretion of urobilinogen is greatly increased and may be several times the normal value. In severe cases the amount excreted daily is equivalent to 8 to 13 Gm. of hemoglobin, amounting in some instances to more than one tenth of the total blood hemoglobin of the body.

2. Following liver therapy and beginning at about the peak of the reticulocyte crisis, there is always a sharp decrease in the excretion of urobilinogen, which falls in a few days to a level within normal limits.

3. In cases of pernicious anemia showing little anemia, with general macrocytosis but little microcytosis or poikilocytosis, the excretion of urobilinogen is increased somewhat above a high normal value. With liver therapy the excretion of urobilinogen falls after a low reticulocyte response and is always normal when the blood picture has become normal

4. The amount of plasma bilirubin in pernicious anemia varies in the same direction as the excretion of urobilinogen and opposite to that of the red blood cell count. It is highest in those patients who are critically ill. When it is high it falls to a normal level during the reticulocyte response.

5. In severe cases of pernicious anemia, urobilin is frequently found in the urine. Large amounts are present only when patients are very ill. Its excess then is attributable, in part at least, to altered liver function.

6. The disturbance in blood pigment metabolism in pernicious anemia is probably due to an abnormality of the red blood cells in virtue of which they suffer early destruction. The abnormal red blood corpuscles present in relapse are the ones most affected. Adequate liver treatment, promoting the production of normal red blood cells, retards the rate at which destruction of the blood occurs and allows the blood picture to become normal.

BRUCELLA INFECTION OF BRIEF DURATION

REPORT OF A CASE *

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MARY POSTON

AND

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Undulant fever is generally considered to be a prolonged recurring disease. Marston,[1] in 1881, reported the average duration to be from three to ten weeks, but recognized a form that he described as so mild that the patient may never be confined to bed and all the while may be supposed to be laboring under a peculiar form of dyspepsia. He gave as diagnostic points in mild types of undulant fever: (1) gastric derangement that refuses to yield to any treatment; (2) great depression of the spirits out of all proportion to the symptoms; (3) slight pyrexial attacks, and (4) anemia, slow and progressive, with a marked tendency to an attack of rheumatism or neuralgia. In describing his own symptoms he probably described one of the earliest ambulatory cases.

Hughes,[2] in his classic monograph published in 1897, disregarded doubtful and nonfatal cases of less than three weeks' duration. Of three hundred and seventy-two cases that he studied, only 1.2 per cent lasted less than twenty days, and all of these were fatal. In his series, the duration of 64.6 per cent of his cases was between thirty-one and ninety days.

Basset-Smith,[3] in 1903, gave three months as the minimum duration, though he stated that in Mediterranean countries the disease may terminate in from one to two months. Eyre,[4] who played a prominent part in the investigations made by the Mediterranean Fever Commission, stated that the duration of the disease is from six to nine months.

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* From the Biological Division of the Medical Clinic of the Johns Hopkins University School of Medicine and Hospital.

1. Marston, A. J.: Report on Fever (Malta), Great Britain Army M. Rep. **3**:507, 1881.

2. Hughes, M. L.: Mediterranean, Malta or Undulant Fever, London, The Macmillan Company, 1897.

3. Basset-Smith, P. W.: Duration of Mediterranean Fever, Brit. M. J. **2**:1589, 1903.

4. Eyre, J. W. H.: Milroy Lectures on Undulant Fever, Lancet **1**:1747, 1908.

There are certain types of cases that run a milder, and sometimes shorter, course than the average. In making studies for the Mediterranean Fever Commission, Shaw [5] investigated a series of ambulatory cases of Malta fever. Samples of blood from five hundred and twenty-five dock hands in Malta were examined. Fifteen per cent of these specimens showed agglutination of *Brucella* in dilutions of 1 : 30 or more, with marked reactions in twenty-two cases. These cases were more thoroughly investigated. In all but three of them there was a history suggestive of mild febrile infection lasting from two days to three months. *Brucella* was recovered from the blood and the urine in three cases, from the blood alone in one case, and from the urine alone in six cases. All of the men studied were working at the time.

Cantani,[6] in Naples, in 1908, described a benign type of Malta fever, discovered by studying the members of families in which more serious forms of the disease were being treated. In one family he noted five cases: one of extreme severity, three moderately severe and one mild. The last occurred in a boy, aged 11, who showed only fever, slight weakness and splenomegaly for a month. His blood serum agglutinated *Brucella* in dilutions up to 1 : 500. Cantani described thirteen cases of this type in other families. The disease in three of his cases, not bacteriologically proved to be cases of undulant fever, lasted only four days. He made the suggestion that the disease is by no means as malignant as is generally supposed, and that more intensive bacteriologic study of the milder cases would probably prove enlightening.

Cantaloube [7] reported sixteen ambulatory cases in 1910, the majority of which were diagnosed by the agglutination reaction. The patients gave a history of several months' illness, with fever, perspiration, more or less generalized pain and constipation. Most of his patients had apparently been infected from eating unpasteurized cheese. He found that this type of infection sometimes persists as long as the more severe form, and that the slight fever may easily go unnoticed unless the temperature is taken systematically. Additional ambulatory and mild cases have been reported by Dargein and Dore [8] and others.

The case to be described is an example of *Brucella* infection with fever of exceptionally short duration.

5. Shaw, E. A.: The Ambulatory Type of Case in Mediterranean or Malta Fever, J. Roy. Army M. Corps **6**:638, 1906.

6. Cantani, A.: Sulle forme leggierissime di febbre di Malta, Riforma med. **24**:365 (April 6) 1908.

7. Cantaloube, P.: Les formes ambulatoires de la fièvre de Malte, Echo méd. de Cevennes, Nimes **11**:22 (Feb.) 1910.

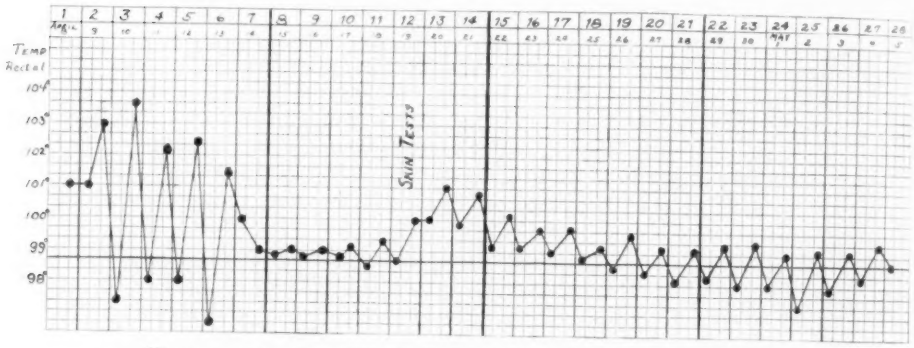
8. Dargein and Dore: Des formes frustes de la melitococcie, Bull. et mém. Soc. de méd. d. hóp. de Paris **49**:122 (Jan. 23) 1925.

REPORT OF CASE

History.—A 25 year old, unmarried physician was admitted to the Isolation Ward of Johns Hopkins Hospital on April 9, 1930, because of fever and general malaise of one day's duration.

For fifteen years he had experienced attacks of migraine preceded by visual aura. During early childhood he had had measles, pertussis and varicella. His tonsils and adenoids had been removed several years prior to the present illness. No other facts of importance in his past history were elicited.

The day before admission he had rather suddenly been seized with headache, anorexia and general malaise, associated with constipation. He spent that afternoon in his room instead of going about his usual duties in the hospital. All of his symptoms became progressively worse, and by evening he noted the onset of aching pains throughout his body, more marked in the lumbar region and in the extremities. Later in the evening he felt worse and was quite prostrated, with increase in the headache and general pain.



The temperature in a case of undulant fever of brief duration. The numerals in the row at the top of the chart represent the days of the disease; those at the left, degrees Fahrenheit.

He had no rhinorrhea, chilliness, sore throat or cough. There were no symptoms referable to the genito-urinary tract.

Physical Examination.—The temperature was 102.6 F.; the pulse rate, 100; the respiration rate, 23; the blood pressure, 138 systolic and 72 diastolic. The patient looked ill and miserable, with flushed cheeks and suffused conjunctivae. The lower eyelids were puffy, but no edema was present elsewhere. No rose spots were found, and there was no rash, although a small aphthous ulcer was present on the buccal mucosa. The venules were dilated in the slightly reddened pharynx. Moderately enlarged lymph nodes were felt in the cervical, epitrochlear, axillary and inguinal regions, but only the right upper deep cervical node was tender. The heart showed no enlargement and was otherwise normal, with the exception of rare extrasystoles.

There was slight impairment of the percussion note over the apex of the left lung, but breath sounds and voice sounds were normal, and no râles were heard even after coughing. The liver was just palpable, but the spleen was not palpable until three days later. Some tenderness was noted over the tibiae, but it was not

marked. The reflexes were normal. At the time of admission influenza seemed the most likely diagnosis.

Laboratory Examination.—The hemoglobin content (Sahli) was 98 per cent; the red blood cells numbered 4,790,000; the white blood cells, 6,760; polymorphonuclear neutrophils, 67 per cent; large lymphocytes, 12 per cent; small lymphocytes, 11 per cent, and large mononuclears, 10 per cent. There were no eosinophils.

The specific gravity of the urine was 1.008. There was a faint trace of albumin. No reducing substances were shown in the urine. The sediment showed red blood corpuscles, 3 per high power field; leukocytes, from 6 to 7 per high power field, and rare granular casts. There was a trace of urobilin. The result of a test for diacetic acid was mildly positive. No growth was obtained on culture of the urine.

In the culture from the throat there were a few beta-hemolytic streptococci, but no diphtheria bacilli.

The blood serum did not agglutinate typhoid or paratyphoid antigens. However, *Brucella* (less than one colony per cubic centimeter) was grown in a blood culture taken on the fourth day of the disease and planted on liver infusion agar of p_H 6.6. The organisms grew as well aerobically as in 10 per cent carbon dioxide, were morphologically characteristic and did not ferment sugars. They agglutinated in serum prepared against a caprine strain of *Brucella* in dilutions up to 1:2,560, in serum prepared against bovine and porcine types in dilutions up to 1:1,280 and in the patient's own serum in dilutions up to 1:1,280.

By the ninth day, which was about the time the organisms recovered from the blood were identified as *Brucella*, the patient's serum agglutinated *Brucella* antigens as follows: a bovine strain in dilutions up to 1:1,280; caprine and porcine strains in dilutions up to 1:640. A blood culture taken at this time showed no growth.

Intradermal tests on the tenth day showed definite cutaneous hypersensitiveness to suspensions of *Brucella* and to extracts of *Brucella* prepared according to the methods of Ando [9] and of Lancefield [10] for isolating the specific soluble substance from bacterial bodies.

Six cultures made from stools collected from the eleventh to the thirtieth day after the onset according to the Amoss and Poston [11] technic did not show *Brucella*, and none was found in five cultures made from the urine.

The white count remained low, never rising to 7,000. On the fifth day, the spleen became palpable. A portable roentgenogram showed the lungs to be clear. Red blood corpuscles persisted in the urine for five days, then disappeared coincidentally with the disappearance of albumin. Nonprotein nitrogen was 26 mg. per hundred cubic centimeters, and sodium chloride was 382 mg. per hundred cubic centimeters of blood.

Course.—The treatment was symptomatic, and after a week the patient's improvement was rapid. Although he was afebrile, with the exception of the

9. Ando, K.: A Simple Method of Obtaining Soluble Specific Substances from Various Bacteria (Streptococcus Viridans, B. Dysenteriae and B. Mallei), J. Immunol. **17**:555 (Dec.) 1929.

10. Lancefield, Rebecca C.: The Antigenic Complex of Streptococcus Hemolyticus: I. Demonstration of a Type-Specific Substance in Extracts of Streptococcus Hemolyticus, J. Exper. Med. **47**:91 (March) 1928.

11. Amoss, H. L., and Poston, M. A.: Isolation of the Brucella Organism from the Stools, J. A. M. A. **93**:170 (July 20) 1929.

mild reaction following the intradermal tests, the patient was kept in bed for four weeks. During the summer, he was somewhat weak, but was able to be up and to play golf from time to time. He was well in October, 1930, and on Feb. 15, 1931, was examined by Dr. Longcope, who found no abnormality.

Origin of Infection.—The origin of his infection was not definitely determined, but the disease was probably contracted in the laboratory. As intern in the Isolation Ward, he had had contact with patients who had undulant fever, but not for two or three months prior to the onset of his own infection. And although he had not worked with *Brucella* in the laboratory for a similar period of time, he frequently visited there. It should be said, however, that no other cases or possible cases of infection with *Brucella* have occurred from this laboratory.

There had been no contact with animals, and the patient had consumed no unpasteurized dairy products.

Bacteriologic Results.—*Brucella* recovered from the patient's blood has not been positively identified as to strain, but the luxuriance of growth even without carbon dioxide suggests the porcine type, as do the reactions to the differential dyes as described by Huddleson.[12] No inoculations of animals have been made.

COMMENT

A case of such short duration as the one reported is interesting from several points of view. The condition might easily have been mistaken for influenza had the blood culture not been taken. It seems possible that a good many cases of the type described pass for cases of some other condition. In several of the ambulatory cases described by Shaw and others there was a history of fever for a short period, and it is probable that a definite relationship exists between the ambulatory cases and those similar to the case under discussion.

It is important to consider patients with ambulatory and abortive cases as possible carriers of *Brucella*. The organism is known to persist in the stools and urine for considerable periods after the acute febrile stage has passed, and we recently[13] reported a case in which *Brucella* was repeatedly cultured from the gallbladder, both on duodenal drainage and at operation. Our patient apparently did not become a carrier. But such a possibility in a mild case might well be of importance from the standpoint of public health. Since the disease does not seem to be highly communicable, the carrier problem need not be overemphasized.

This case may also explain the cutaneous hypersensitiveness to *Brucella* and the presence of agglutinins for *Brucella* that have been described by many observers in patients with no history of undulant fever.

12. Huddleson, I. F.: The Differentiation of the Species of the Genus Brucella, Techn. Bull. 100, Michigan State Coll. Agric. Exper. Sta., August, 1929.

13. Leavell, H. R., and Amoss, H. L.: Brucella Infection: Cultivation of Brucella from the Bile: Case Report, Am. J. M. Sc. **181**:96, 1931.

SUMMARY

1. A case of *Brucella* infection with fever of seven days' duration is presented.

2. The possible significance of cases of such short duration is discussed with regard to the possibility that the patients in whom they occur might subsequently become carriers, and with regard to the development of cutaneous hypersensitiveness to *Brucella* and of agglutinins for *Brucella* antigens.

3. The difficulty of diagnosing such a case by ordinary clinical methods is pointed out.

THE ENDERMIC REACTION IN BRUCELLA INFECTIONS *

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The endermic reaction for *Brucella* infection has been used for the most part as a confirmatory test. But Burnet [1] and others have reported positive cutaneous reactions in cases in which the blood serum showed no agglutination with *Brucella* and in which the blood cultures were negative.

Various antigens have been used in testing for cutaneous hypersensitiveness to *Brucella* and its products. These antigens may be classified roughly into two groups: (1) bacterial suspensions and (2) filtrates of broth cultures.

The use of the filtrate of a broth culture from twenty to thirty days old was described in 1922 by Burnet,[2] who called the substance "melitin." It has since been widely used, particularly in countries bordering on the Mediterranean, and the results have varied. Trenti [3] in 1923 reported specific reactions in nine cases of undulant fever, with negative results in forty controls. Olmer and Massot,[4] Debré, Marie and Giroud,[5] Lemierre, Marchal and Jaubert,[6] Cazalas [7] and Liege and Casteran [8] reported about sixty additional cases of undulant fever in

* Submitted for publication, Feb. 24, 1931.

* From the Biological Division of the Medical Clinic of the Johns Hopkins University School of Medicine and Hospital.

1. Burnet, E.: Diagnosis of Mediterranean Fever by the Intradermal Reaction: Action of the Filtrate of Culture of M. Melitensis, Arch. Inst. Pasteur de l'Afrique du Nord **2**:187, 1922.

2. Burnet, E.: A New Method of Diagnosing Malta Fever, Compt. rend. Acad. d. sc. **174**:421 (Feb. 6) 1922.

3. Trenti, E.: The Value of the Intradermal Reaction in Melitensis Infections, Policlinico (sez. prat.) **32**:767 (June 1) 1925.

4. Olmer, D., and Massot, M.: On the Diagnosis of Malta Fever by the Intradermal Reaction, Marseille méd. **61**:1206 (Oct. 25) 1924. Olmer, D.: Burnet's Melitin, J. méd. franç. **18**:182 (May) 1929.

5. Debré, R.; Marie, J., and Giroud, P.: Autochthonous Undulant Fever: Burnet's Melitin Test, Bull. et mém. Soc. méd. d. hôp. de Paris **51**:1654, 1927.

6. Lemierre, A.; Marchal, C., and Jaubert, A.: A Case of Autochthonous Undulant Fever; Diagnostic and Therapeutic Value of Burnet's Intradermal Reaction, Bull. et mém. Soc. méd. d. hôp. de Paris **51**:1702 (Dec. 29) 1927.

7. Cazalas, X.: A Case of Undulant Fever, Paris méd. **18**:161 (Aug. 25) 1928.

8. Liege, R., and Casteran, R.: A New Case of Malta Fever Cured by a Single Injection of an Endoprotein Prepared from B. Abortus Bang, Gaz. d. hôp. **102**:41 (Jan. 9) 1929.

which specific reactions were obtained, using melitin. Their control groups, however, were small.

Schoenholz and Meyer [9] used a product similar to melitin which they called "abortin," with apparently satisfactory results, as did Huddleson and Johnson.[10]

Another group of investigators has hesitated to accept the reaction to melitin as a specific reaction, but has acknowledged its possible usefulness. Brugi [11] reported positive results in 38 per cent of sixty control cases in which Burnet filtrate had been used. Tapia and del Valle [12] used both bacterial suspension and melitin. They observed positive reactions with both in seven of fourteen cases of undulant fever, with melitin alone in two, and with the suspension alone in five. They made seventy-one control injections. The filtrate gave false positive reactions in 25 per cent of these; the suspension gave such reactions in only 7 per cent. Sorge [13] found positive reactions in 27 per cent of eighty-six controls with melitin. Agglutination of *Brucella* was negative in all but one of these positively reacting controls, and in that case it occurred only in the dilution of 1:80. More recently, Duffau [14] obtained 16 per cent false positive reactions in seventy controls, both the filtrate and the suspension being used, but considered the reactions with the filtrate to be somewhat sharper.

Mitra,[15] Fornaco and Bua-Fazio,[16] deFermo,[17] Giordano [18] and Simpson and Frazier [19] found the bacterial suspension to be superior

9. Schoenholz, P., and Meyer, K. F.: The Purification of Abortin, J. Infect. Dis. **40**:453 (March) 1927.

10. Huddleson, I. F., and Johnson, H. W.: Brucellosis: The Significance of Brucella Agglutinins in the Blood of Veterinarians, J. A. M. A. **94**:1905 (June 14) 1930.

11. Brugi, A.: The Burnet Intradermal Reaction in Malta Fever Infection, Pensiero med. **13**:361 (July 20) 1924.

12. Tapia, M., and del Valle, A.: Diagnostic Value of the Cutaneous Reaction with Specific Antigen in Malta Fever, Med. ibera **22**:317 (Oct. 13) 1928.

13. Sorge, G.: The Value of the Intradermal Reaction in Malta Fever Infection of Children, Riv. di clin. pediat. **23**:471 (July) 1925.

14. Duffau: The Utilization of the Laboratory in the Diagnosis of Undulant Fever, Arch. Inst. Pasteur d'Algérie, 1928, vol. 6, no. 4.

15. Mitra, M.: The Intradermal Reaction in Mediterranean Fever of Infancy, Pediatria **32**:721 (June 15) 1924.

16. Fornaco, L., and Bua-Fazio, F.: The Intradermal Reaction for the Diagnosis of Malta Fever, Riforma med. **40**:393 (April 28) 1924. Bua, F.: Method and Value of Intradermal Reaction in Malta Fever, Minerva med. **6**:394 (May 20) 1926.

17. de Fermo, C.: Method and Value of the Intradermal Reaction in Malta Fever, Gaz. d. osp., Turin **48**:859 (Sept. 11) 1927.

18. Giordano, A. S.: Brucella Abortus Infection in Man: The Intradermal Reaction as an Aid in Diagnosis, J. A. M. A. **93**:1957 (Dec. 21) 1929.

19. Simpson, W. M., and Frazier, E.: Undulant Fever, Report of Sixty-Three Cases Occurring in and About Dayton, Ohio, J. A. M. A. **93**:1958 (Dec. 21) 1929.

to the filtrate. In two hundred and sixty-nine controls, they found positive reactions in only a negligible percentage, although in cases of undulant fever they never failed to obtain strongly positive reactions.

All observers who have had any experience with the endermic reaction have reported a high percentage of positive results in cases of undulant fever, more or less regardless of the type of antigen used.

The specificity of the tests has been the subject of the greatest contention. The consensus seems to be that the bacterial suspension gives fewer false positive reactions than the filtrate. In fact, only a few false positive reactions with the suspension have been reported.

EXPERIMENTS

Intracutaneous tests were made in a small group of cases of undulant fever and in fifty-one controls. In addition to the antigens previously used, a saline extract was employed, prepared by shaking a suspension of *Brucella* in a shaking machine for forty-eight hours and then centrifugating it for one hour.

Attempts were made to isolate the so-called "specific soluble substance" according to the methods described for streptococci by Lancefield [20] and Ando.[21]

Bacterial suspensions were standardized by comparison of turbidity with the 1:1,000 United States Public Health silica standard and were heat killed. In the later tests, this standard suspension was diluted with saline solution 1:10 and 1:100, to decrease, if possible, the number of false positive reactions and to titrate the degree of cutaneous hypersensitiveness, as is done in the tuberculin reaction.

A relatively large number of different preparations made from several strains of *Brucella* were used in testing each case or control. For this reason, although the number of cases and controls is not great, a rather large number of injections were made—587 in all; an average of 9.6 in each person studied, and in none less than 6.

The reactions were read from eighteen to twenty-four hours after the injections, and classified, according to the size of the zones of erythema, as follows: reactions with zones of erythema measuring up to 0.7 cm., 0; from 0.8 to 0.9 cm., ±; from 1 to 1.4 cm., +; from 1.5 to 1.9 cm., ++; from 2 to 2.4 cm., +++, and 2.5 cm. or more, ++++.

Although central necrosis resulted more frequently and was more marked in the cases of undulant fever, it was also present in the control group.

In classifying the results of endermic tests in any given case, the reactions to all the substances, rather than that to any one extract, used in that case, were considered.

A summary of the results is shown in table 1. The case of "possible undulant fever" occurred in a patient with a suggestive history, but

20. Lancefield, Rebecca C.: The Antigenic Complex of Streptococcus Hemolyticus: I. Demonstration of a Type-Specific Substance in Extracts of Streptococcus Hemolyticus, J. Exper. Med. **47**:91 (March) 1928.

21. Ando, K.: A Simple Method of Obtaining Soluble Specific Substances from Various Bacteria (Streptococcus Viridans, B. Dysenteriae, and B. Mallei), J. Immunol. **17**:555 (Dec.) 1929.

the cultures and the results of the tests for agglutinins in the blood serum were negative. All the other cases of undulant fever were proved bacteriologically to be definitely positive.

The group classified as "other unrelated diseases" was composed of cases of hypertension, arteriosclerosis, chronic arthritis (not apparently due to *Brucella*), duodenal ulcer, amebiasis, Hodgkin's disease, leukemia, aortic aneurysm, syphilis, lead poisoning, diabetes, abscess of the lung, meningitis due to *Streptococcus viridans*, erythremia,

TABLE 1.—*Results of Endermic Tests According to Diagnosis*

Diagnosis	Cases	Reactions		
		Positive, %	Questionable, %	Negative, %
Undulant fever	9	78	22	0
Possible undulant fever	1*	100	0	0
Tuberculosis	6	33	66	0
Typhoid fever	2	0	50	50
Normal	12	25	33	42
Other unrelated diseases	31	18	38	44

* A physician who had lived in a Mediterranean country as a child and who in college had worked with fresh embryos from pigs.

TABLE 2.—*Results of Endermic Tests According to Preparation Used*

Preparation	Cases	Reactions		
		Correct, %	Questionable, %	False, %
Porcine suspension	63	57	18	25
1: 100 dilution of porcine suspension	25	80	12	8
Porcine saline extract	36	80	14	6
Porcine Ando extract	13	54	31	15
Porcine Lancefield extract	13	54	23	23
Bovine suspension	62	45	20	35
Bovine saline extract	34	62	27	11
Bovine Ando extract	12	42	16	42
Bovine Lancefield extract	13	84	..	16
Caprine suspension	57	47	28	25
1: 100 dilution of caprine suspension	25	92	4	4
Caprine saline extract	23	79	21	..
Caprine Ando extract	13	80	..	20
Caprine Lancefield extract	13	61	23	16

bronchial asthma, cholecystitis and hyperthyroidism. No definite relationship could be found between the type of disease and the positive reaction in the control group.

Although twenty-two different preparations were studied, only fourteen were used in a sufficient number of cases to be tabulated. So many false positive reactions were obtained with filtrates of broth cultures that their use was abandoned early in the series.

The diluted saline suspensions and the saline extracts gave better results than the other preparations; the extracts prepared after the methods of Ando and of Lancefield gave somewhat better results than

the simple standard suspensions. It can be readily seen that none of the substances gave uniformly satisfactory results, and apparently a high percentage of correct reactions is the best that can be hoped for.

COMMENT

It is obviously of the greatest importance to evaluate the endermic test as a diagnostic measure. It is a procedure that is relatively simple and that requires little apparatus after the antigens are prepared. Therefore it is widely applicable even in isolated districts. However, the interpretation of the reactions is not uniformly simple, and unless certain precautions are used the results may be misleading.

The cutaneous hypersensitiveness observed by us in cases of undulant fever has varied from time to time in the course of the disease, and we are unable to lay down definite rules for this variation. Certain patients have been more reactive in the early stages of the disease, while of others the reverse has been true. Some persons have reacted more violently to certain strains of *Brucella* than to others, and the strain producing the most marked intracutaneous reaction has not always been of the same type as the one with which the patient was infected.

The injection of antigen for an endermic test brings with it the possibility of producing agglutinins that may complicate the diagnostic picture. This was described by Giordano and confirmed in the case of one of us, whose serum about six weeks after a series of endermic tests agglutinated *Brucella* in dilutions up to 1:1,280 although no agglutinins had been demonstrated previously.

The "erythema brucellum" described by Huddleson and Johnson,[10] which occurred in veterinarians who had tended cows with contagious abortion is interesting in the study of cutaneous hypersensitiveness to *Brucella*. They described two types: one an urticaria-like lesion of short duration; the other a papular erythema lasting from three to four days. They found agglutinins with titers of 1:50 and 1:100 in the five men tested, who had manifested this erythema following the manual extraction of retained placentas in aborting cows. When endermic tests with *Brucella* filtrates were made, these men showed a prompt reaction, reaching a maximum in six hours. Other patients who had not shown the erythema, but who had had even higher titers of agglutination, showed a much less marked and more delayed cutaneous reaction to the filtrate. This is additional evidence that the cutaneous reaction may produce variable results in different persons.

CONCLUSIONS

1. The endermic reaction is of value in the diagnosis of undulant fever, particularly in cases in which no agglutinins for *Brucella* are

present in the blood serum and in which *Brucella* cannot be grown on culture of the blood, urine, stools or bile.

2. The intracutaneous test is not definitely specific. Although the result is generally positive in undulant fever, it is not infrequently positive, or highly suggestive, in controls.

3. Representative strains of several different types of *Brucella* should be used in making the test. The interpretation of the test should be based on all the reactions rather than on a single one.

4. Extracts of *Brucella* prepared according to the methods of Lancefield and of Ando for securing the soluble specific substance gave no more specific results in our cases than did the simple saline suspensions and extracts.

5. It is probable that an extract of *Brucella* prepared by prolonged shaking of a saline suspension, followed by centrifugation to remove most of the organisms, gives fewer false reactions than other preparations. But such a preparation does not always give a positive reaction in undulant fever.

6. Heat-killed bacterial suspensions seem to have more specific action than bacterial filtrates.

7. It is of value to titrate the degree of the endermic reaction by using varying dilutions of suspensions of the strains being tested, as in the tuberculin reaction.

PEPTIC ULCER

ASSOCIATION WITH PULMONARY TUBERCULOSIS *

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In 1926 we published a portion of a study of all the peptic ulcers recorded in 7,700 necropsy records in Bellevue Hospital.[1] The part then published dealt with frequency, number, size, shape, location, color, sex and age. This article is a continuation of that study and will record the association of peptic ulcer with tuberculosis.

Fifteen years after Cruvelhier's original description of gastric ulcer, von Jaksch,[2] in 1844, reported that of his patients afflicted with gastric ulcer one-fifth were tuberculous. Dittrich,[3] the same year, mentioned a similar connection. Nine years later, Engel[4] found 19 per cent. In 1864, Brinton[5] quoted these figures but felt that the association of gastric ulcer with other diseases is "in proportion more akin to their known frequency, than to other of their circumstances." He pointed out that deaths from phthisis are rather more than 18 per cent of deaths from all diseases in persons over 20 years of age. Leube,[6] in 1876, commented on this association and quoted von Jaksch, Dittrich and the figures of Steiner, who found phthisis 33 times in a series of 110 necropsies in which open and healed gastric ulcers were found. He also quoted Wollmar who found in a series of 48 necropsies only 5 instances of phthisis. Leube thought that larger series should be studied and that the association of ulcer and tuberculosis was not proved. In 1894, Perry and Shaw[7] published their much quoted study of the findings on

* Submitted for publication, Feb. 23, 1931.

* From the Department of Medicine, the University and Bellevue Hospital Medical College, New York University, and the Third Medical Division, Bellevue Hospital.

1. Sturtevant, M., and Shapiro, L. L.: Gastric and Duodenal Ulcers, Arch. Int. Med. **38**:41 (July) 1926.

2. von Jaksch: Beitrag zur Lehre vom perforierenden Magengeschwür, Prag. Vierteljahrschr. **3**:1, 1844.

3. Dittrich, in Papellier: Tuberculosis von Magengeschwür, 1854.

4. Engel: Ueber Geschwüre, Schmidt's Jahrb. **82**:237, 1854.

5. Brinton, W.: Lectures on Diseases of the Stomach, ed. 2, London, 1864, p. 155.

6. Leube, W. O.: Diseases of the Stomach, in Ziemssen: Cyclopedia, 1878, vol. 7.

7. Perry, E. C., and Shaw, L. E.: Guy's Hosp. Rep. **1**:171, 1894.

duodenal ulcer in 17,652 necropsies. Among these they collected 70 cases of duodenal ulcer, 25 of which were associated with tuberculosis. Thus we have the pathologists noting the association of ulcer and tuberculosis, and the clinicians, for the most part, doubting any connection between these two disorders.

Fox [8] remarked the absence of gastric ulcer in cases of tuberculosis that he had studied. Fenwick [9] said that since 18 per cent of persons have tuberculosis, naturally 18 per cent of persons with gastric ulcer have tuberculosis. He found 9 cases of ulcer of the stomach in 1,000 autopsies on tuberculous patients and, using Welch's statistics that gastric ulcer occurs in 2 per cent of all diseases, he figured that ulcer is less common in tuberculosis than in other diseases. McFarland [10] believed that the presence of peptic ulcer in the dead is usually quite independent of the disease from which the patient dies. Hauser [11] also doubted that tuberculosis has any special etiologic effect. Collinson and Stewart [12] felt that the theory of a tuberculous etiology has never received much support. They found 86 cases of tuberculosis in 1,000 unselected necropsies (8.6 per cent). In 151 necropsies on persons with peptic ulcer there were but 5 cases of tuberculosis (3.4 per cent), and when the series was extended to include ulcer scars, of the 282 cases there were but 8 associated with tuberculosis, reducing the percentage to 2.1. Lisa [13] found 9 ulcers in 257 necropsies on tuberculous subjects and 4 ulcers in 209 nontuberculous patients. Emery and Monroe [14] reported a clinical series from the Peter Bent Brigham Hospital. Of this series of patients 5.4 per cent suffered from pulmonary tuberculosis; 18 of the 30 cases were considered inactive tuberculosis. These authors thought that the tuberculosis did not influence the course of the ulcer and that there was no greater association of the two diseases than one would expect. In two books recently published in this country Rehfus [15] did

8. Fox, W.: Diseases of the Lungs and Pleura, London, J. & A. Churchill, 1891, p. 606.

9. Fenwick, W. Soltau: The Dyspepsia of Phthisis, London, H. K. Lewis, 1894, p. 33.

10. McFarland, J.: Surgical Pathology, Philadelphia, P. Blakiston's Son & Co., 1924, p. 564.

11. Hauser, G.: Die peptischen Schädigungen des Magens des Duodenums und der Speiseröhre und des peptische postoperative Jejunalgeschwür, in Henke and Lubarsch: Handbuch der speziellen pathologischen Anatomie und Histologie, Berlin, Julius Springer, 1926, vol. 4, p. 339.

12. Collinson, H., and Stewart, M. J.: Chronic Peptic Ulcer of the Stomach with Acute Miliary Tuberculosis of the Gastric Mucosa, Brit. J. Surg. **15**:626 (April) 1928.

13. Lisa, J. R.: Surg., Gynec. & Obst. **41**:664 (Nov.) 1925.

14. Emery, E. S., and Monroe, R. T.: Peptic Ulcer, Arch. Int. Med. **43**:846 (June) 1929.

15. Rehfus, M. E.: Diagnosis and Treatment of Diseases of the Stomach, Philadelphia, W. B. Saunders Company, 1927.

not mention this association, and Crohn [16] said: "A coincidence of the two conditions ulcer and phthisis is inevitable when one considers the wide incidence of both in the adult population."

Attempts to explain an association between peptic ulcer and tuberculosis are occasionally found. Arloing [17] suggested that the toxin of tuberculosis might be an etiologic factor in the production of ulcer of the stomach. Kodon [18] studied patients with ulcer, their mode of living and their family history. He found tuberculosis in a severe form in the families of 49 patients afflicted with ulcer, and in 5 different families he found tuberculous lesions of the skin. Kodon could not resist the thought that tuberculous infection must have some connection with round ulcer of the stomach. Stiller [19] believed that there is a connection, but thought that both conditions are the result of the asthenic constitution. He found hyperacidity, chlorosis and atony of the stomach associated with tuberculosis and ulcer. Meyer [20] approached the subject from still a different angle. He pointed out the frequency of dyspeptic symptoms in the tuberculous and studied 50 cases of pulmonary tuberculosis with severe gastric symptoms. Among these he found 4 definite and 2 suspected cases of duodenal ulcer. He suggested that not only may tuberculosis predispose to peptic ulcer but that such ulcers, thus formed, are more likely to become chronic.

Since sufficient evidence has been accumulated to make the coexistence of peptic ulcer and tuberculosis of a possible, if not indeed a probable, frequency beyond what one should reasonably expect even in two disorders so commonly found, we have thought it worth while to tabulate findings on this association in 7,700 necropsies at Bellevue Hospital and apply the ordinary statistical tests to the figures obtained. The standard error has been figured after the formula $\sqrt{\frac{p\,q}{n}}$ in which p is a fraction whose numerator is the number of the sample showing deviation and whose denominator is the number of cases in the whole sample, q is the complement of that fraction and n is the number of cases in the sample. The standard error of the difference of two rates is figured as the square root of the sums of the squares of the standard errors of the two rates.

16. Crohn, B. B.: Affections of the Stomach, Philadelphia, W. B. Saunders Company, 1927.

17. Arloing: Des ulcérations tuberculeuses de l'estomac, Paris, Asselin & Honzeau, 1903.

18. Kodon, E.: Ein Erklärungsversuch der Pathogenese des Ulcus rotundumventriculi, Wien. med. Wchnschr. **60**:1992, 1910.

19. Stiller, B.: Magengeschwür und Lungentuberkulose, Berl. klin. Wchnschr. **48**:325 (Feb. 20) 1911.

20. Meyer, J.: Peptic Ulcer Complicating Pulmonary Tuberculosis, Illinois M. J. **46**:348 (Nov.) 1924.

Our study of 7,700 necropsies at Bellevue Hospital [1] showed the incidence of gastric ulcer and scars to be 120, and of duodenal ulcer and scars 44. There were 86 open gastric ulcers and 35 open duodenal ulcers. Deducting for open duodenal and gastric ulcers in the same person, there were 117 cases of peptic ulcer.

Among the 7,700 necropsies studied, 891 patients were recorded as having active pulmonary tuberculosis; this is an incidence of 11.57 ± 0.36 per cent. Among the 120 patients with gastric ulcers and scars there were 43 who had suffered from active pulmonary tuberculosis at the time of death, an incidence of 35.83 ± 4.4 per cent. To be significant, the difference between the incidence of tuberculosis in the ulcer sample and in the whole sample must be over twice the standard error of the difference. The difference is 24.26 ± 4.4 per cent, which is, of course, highly significant.

Or if we reject the cases of healed ulcer as possibly misleading, in that these ulcers may have existed and healed before the onset of the tuberculosis, we find that there were twenty-eight tuberculous subjects among the eighty-six with open ulcer. This is an incidence of 32.55 ± 5.05 per cent. The incidence of active tuberculosis in the whole sample is, as already stated, 11.57 ± 0.36 per cent, so that here the difference is 20.98 ± 5.06 per cent, which is more than twice the standard error of the difference.

Of 44 patients showing at necropsy either healed or open duodenal ulcers, 10 had active tuberculosis. Two of these patients had tuberculous meningitis without discovered pulmonary tuberculosis. Disregarding the cases of meningitis, there were 8 tuberculous subjects in the group of 44, an incidence of 18.18 ± 5.8 per cent. The incidence of tuberculosis in 7,700 necropsies was 11.57 ± 0.36 per cent, and the difference was 6.61 ± 5.8 per cent, which is far short of twice the standard error of the difference. We therefore feel that our duodenal ulcer sample is too small to be significant.

However, if we combine the cases of unhealed duodenal ulcer and those of unhealed gastric ulcer found in the 7,700 necropsies, deducting for cases in which gastric and duodenal ulcers were coexistent, we have 117 cases of peptic ulcer. There were 33 instances of pulmonary tuberculosis in this sample, or 28.21 ± 4.1 per cent. The difference between the incidence of tuberculosis in the cases of peptic ulcer and in the whole sample studied would be 16.64 ± 4.1 per cent. This again is a marked difference, much more than twice its standard error.

Similarly, if we compare the incidence of ulcer of the stomach in all necropsies, 86 in 7,700 (1.12 ± 0.12 per cent), with the incidence of ulcer of the stomach in the necropsies showing tuberculosis, 28 in 891 (3.14 ± 0.58 per cent), the difference is 2.02 ± 0.59 per cent, which is well over twice the standard error. Or if we compare the frequency of peptic ulcers in the whole sample, 117 in 7,700 (1.52 ± 0.14 per cent),

with the frequency in the tuberculous group, 33 in 891 (3.7 ± 0.63 per cent), we have a difference of 2.18 ± 0.64 per cent.

Further striking association is shown in other groups of pulmonary and pleural diseases. Thirty patients described as having chronic adhesive pleurisy were among the eighty-six with open gastric ulcers. Thirteen of these, however, were patients having active pulmonary tuberculosis, and of the remainder a certain number were undoubtedly tuberculous.

Pneumonia has been mentioned as associated with ulcer.[2] Nine cases of lobar pneumonia were found among the eighty-six patients with open ulcers who were not suffering from active tuberculosis. Likewise eleven patients with neither tuberculosis nor lobar pneumonia had bronchopneumonia. The bronchopneumonia was, for the most part, a terminal condition complicating disease of the kidney or heart or other illnesses that might predispose to ulcer. It is difficult to see how lobar pneumonia, a disease of comparatively short duration, could have had anything to do with the pathogenesis of chronic ulcers of long standing. It is possible that ulcers may predispose to pneumonia or that they are, for similar or different reasons, to be found in a particular constitutional panel.

Bronchitis and emphysema were also frequently mentioned in association with peptic ulcer. It was impossible to separate a bronchitis or emphysema group of such purity and size as to be significant. These associations were striking enough, however, to suggest that some common factor in pulmonary disease might predispose to ulcer or that ulcer might predispose to pulmonary disease. An example of a common factor in pulmonary disease would be cough. It is known that vomiting is a cause of gastric erosions.[21] Cough is similar physiologically, is accompanied by marked alterations in intra-abdominal pressure and may be accompanied by vomiting, if severe and prolonged. A possible mechanism for ulcer as an incident in pulmonary disease is suggested by the early exaggerated parasympathetic tonus seen in tuberculous disease.[22] Constitutional predisposition to diseases that are themselves otherwise unrelated is possible.

SUMMARY

A review of the literature of the association between peptic ulcer and tuberculosis is given, showing great difference of opinion. Figures obtained from a study of 7,700 necropsies at Bellevue Hospital are presented, which reveal a definitely increased frequency of peptic ulcer in tuberculosis. This frequency is shown to be statistically sound.

21. Aschoff, L.: Lectures on Pathology, New York, Paul B. Hoeber, Inc., 1924, p. 290.

22. Kuntz, A.: The Autonomic Nervous System, Philadelphia, Lea & Febiger, 1929.

CONGESTIVE HEART FAILURE

XI. THE EFFECT OF DIGITALIS ON THE DYSPNEA AND ON THE VENTILATION OF AMBULATORY PATIENTS WITH REGULAR CARDIAC RHYTHM *

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Digitalis has been used in the treatment of cardiac disease for nearly a century and a half, but there is still no general agreement as to when it should be given. Although a complete review of the literature will not be attempted, the following brief résumé will suffice to illustrate some of the disputed points. For the sake of clarity it should be stated here that the term "regular rhythm" as used in this paper includes persons who have sino-auricular rhythm either with or without premature beats.

1. *Is digitalis of value in auricular fibrillation?* All authors agree on an affirmative answer.

2. *Is digitalis ever of value in patients with regular rhythm?* Sir James Mackenzie (1920) believed that the drug was of little value except in patients with auricular fibrillation. Later (1925), however, he stated, in speaking of cardiac failure without valvular disease and with regular rhythm: "Without why or wherefore, drugs of the digitalis group occasionally have a good effect." Vaquez (1924) believed that while digitalis is of great value in auricular fibrillation, its value is much less than that of strophanthus in patients with regular rhythm. He thought that although digitalis acts as well as or better than strophanthus on the auriculoventricular node, the latter drug had a much greater tonic effect on the heart and hence was much better in patients with paroxysmal dyspnea.

On the other hand, Christian (1918, 1919, 1925) insisted that digitalis is of great value in patients with regular rhythm. Most authors agree with this opinion to the extent of believing that the drug is bene-

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ficial under certain conditions in such patients (Rosenbach [1897], Broadbent [1900], Cushny [1911], Cohn [1915], Osler [1919], Pratt and West [1920]).

3. *Is digitalis of value in patients with regular rhythm and with edema (right ventricular failure)?* Mackenzie (1920) claimed that such benefit as was observed was due to a diuretic action, and this appears to have been Withering's view. Most other authors, however, believe that the beneficial diuretic action in such cases is secondary to the drug's effect on the heart. In summarizing opinions in this matter Robinson (1923) stated: "There is general agreement that in cases of myocardial insufficiency with edema, diuresis follows the administration of digitalis, the edema is diminished or disappears and there is general improvement in symptoms." In his well controlled study, Marvin (1927) pointed out that in cases with regular rhythm and edema, digitalis is most effective in subjects with arteriosclerotic heart disease and least effective in patients with rheumatic disease, persons with syphilitic disease being intermediate in this respect.

4. *Is digitalis of value in patients with regular rhythm without edema and with cardiac asthma (left ventricular failure)?* Concerning this point many authors make no positive statements. The reason for lack of certainty in this regard probably is the fact that, while changes in the urine volume and the body weight allow one to make a decision based on quantitative determinations of the effect of a given measure on the degree of edema, conclusions in regard to dyspnea, which is a subjective phenomenon, are attended with more difficulty.

Many authors advocate giving digitalis whenever there is a "break in compensation," but, as they do not define the term, one is left in doubt as to whether or not they consider paroxysmal dyspnea as an indication for the drug. However, some authors are more specific. Rosenbach claimed that digitalis was of value in cardiac asthma. Broadbent, Hirschfelder (1913) and Osler insisted on the value of digitalis in cases of left as well as right ventricular failure. On the other hand, Vaquez stated that digitalis is far inferior to ouabain in this regard. Cohn, Robinson and Gibson (1927) stated that the effects of the drug are less beneficial in patients without edema than in those with edema. Mackenzie at one time denied, but later affirmed, the value of the drug in the cases under discussion.

5. *Is digitalis of value in patients with diminished cardiac reserve but without congestive failure?* (We use the phrase "diminished cardiac reserve but without congestive failure" to indicate the state in which a patient has no discomfort at rest—no orthopnea, paroxysmal dyspnea or edema—but experiences dyspnea on the performance of an exertion

which he could previously do with ease.) In patients who, having had congestive failure, regain compensation, Eggleston (1925) and Christian (1925) advocated the continued use of small doses of the drug. Probably most cardiologists, in America at least, agree with this view. But when is one to start digitalis in a patient who has never had symptoms at rest but who is beginning to have dyspnea with exercise? Christian (1925) stated that the drug is usually contraindicated when symptoms are slight or absent, but should be given if symptoms are increasing in severity. Neither Osler, Robinson nor Cohn apparently believed in giving the drug until decompensation supervened. Hirschfelder thought that digitalis should be given whenever there was dilatation, regardless of whether or not signs of decompensation were present. Cushny (1925) stated:

> It is difficult to determine at what stage of insufficiency digitalis treatment should be commenced. It is obviously unnecessary in the slighter forms such as are indicated by some breathlessness after exertion, which is so common in advancing years. At the same time there should be no hesitancy in prescribing it when the circulation is more distinctly strained. Small doses may be tried without any apprehension that they may induce unpleasant symptoms; and no tolerance is acquired in practice, so that its early exhibition does not prejudice its use when advance in the insufficiency demands treatment more imperatively. At present this use of digitalis must be regarded as merely tentative until the indications for its use are more definitely determined.

As a result of their demonstration that digitalis caused a diminution in the output of the heart in dogs, Harrison and Leonard (1926) believed that the drug might be of value in preventing, as well as in combating, congestive failure.

6. *Is digitalis of value in patients with cardiac disease without diminution of cardiac reserve, i. e., without symptoms?* There seems to be agreement by all authors that the drug is not indicated under such conditions.

One may summarize the foregoing review by saying that there is universal agreement concerning the benefit to be derived from digitalis in patients with auricular fibrillation, and almost as great unanimity in regard to its value in many cases with regular rhythm and edema, but that there is considerable diversity of opinion concerning its effect in patients with paroxysmal dyspnea and in regard to the question of when, if at all, it should be administered to patients whose only cardiac symptom is dyspnea on exertion. The present study was undertaken in an endeavor to elucidate the unsettled problems just mentioned. Interest has been particularly centered on the effect of digitalis in patients with paroxysmal dyspnea.

METHOD

All patients were ambulatory. Subjects with more than slight edema and subjects with cardiac neurosis were excluded from the series. In all cases there was demonstrable cardiac enlargement. The majority of the patients had hypertension, arteriosclerosis or syphilitic aortitis as the cause of their cardiac disorders. There were only two cases of rheumatic disease. In three patients the underlying cause could not be determined and such cases were classified simply as cardiac enlargement. Several patients had two or more possible etiologic factors and were classified according to which factor seemed most important.

Dyspnea was present in every patient, and was usually the chief and sometimes the only symptom. In twenty-four cases, dyspnea with exertion only was complained of, whereas nineteen patients, in addition to having dyspnea with exercise, also had paroxysmal attacks of shortness of breath, usually at night. At each visit a record was made of the frequency and duration of such attacks.

The desired plan consisted in prescribing digitalis without instituting any other therapeutic measure whatever, without changing the patient's activities, without limiting fluids, without altering his diet and without prescribing sedatives. This plan was not strictly adhered to, as the patient's symptoms sometimes demanded other therapy, but in thirty-eight of the forty-three patients no therapy other than digitalis was given. The drug was administered in the form of capsules or tablets of the powdered leaf. The most frequent dosage was 0.6 Gm. daily for three days and then 0.2 Gm. daily for an indefinite period. In several cases the initial dose was 1 Gm. daily for two days, and in one instance the patient was given 2 Gm. at a single dose. The general plan was to give from 1.5 to 2 Gm. in the first three days and from 2.5 to 3 Gm. in the first week. No serious toxic symptoms resulted in any case, although nausea occurred occasionally and vomiting rarely. Electrocardiograms were made in some patients but not in all of them. As our interest was in subjective rather than objective phenomena, no attempt was made to control our therapy by frequent electrocardiograms. Teleoroentgenograms were made in all cases in which the question of the presence or absence of cardiac enlargement could not be definitely answered by physical examination. The majority of the patients were seen in the medical outpatient department of the Vanderbilt University Hospital, but a few patients treated by one of us in private practice are included. Most of the patients included in the series were followed from three to six months. A few patients were observed for periods of several weeks only, and a few of them have been followed for two years or more. In going over the records we have attempted to be conservative in ascribing improvement to digitalis. When there was

any reasonable doubt from the patient's statements as to whether he was benefited we have regarded the condition as unimproved. Two of us tabulated the results separately; the data were then combined and for each patient the tabulation which showed the least improvement was adopted. It is obvious that when a patient states that a given symptom has disappeared the chances for error are slight, whereas when he states that the symptom is better but still present, the chances for error are greater.

The term "paroxysmal nocturnal dyspnea" as used in this paper refers to attacks of shortness of breath which wake the patient up, and is not to be confused with orthopnea, an allied but not identical symptom.

It soon became obvious from the records of the patients' symptoms that the effect of digitalis in patients with paroxysmal dyspnea was so striking as to leave little question as to its value. In patients with dyspnea on exertion only, the results were much less dramatic and, although many patients seemed to think they were benefited, we were in doubt as to how much of this subjective improvement was real and how much was imaginary. Consequently, it seemed necessary to devise some means of achieving a quantitative expression of dyspnea.

Such a method was developed and has been described in the preceding paper in this series. This method consisted, in brief, of measuring the vital capacity and the ventilation during and after a series of carefully standardized exercises. The ventilation was divided by the vital capacity and multiplied by a correction factor for the body weight. The figure arrived at in this way was called the ventilation index. In order to determine objectively whether digitalis actually does cause improvement in dyspnea on exertion, respiratory measurements were made in eight patients before and after digitalis was given.

RESULTS

The Effect of Digitalis on Paroxysmal Nocturnal Dyspnea.—The reports of the subjective conditions of nineteen subjects with this symptom are shown in table 1. One patient was worse after digitalis, two subjects were better and sixteen of the nineteen persons were entirely relieved. The effect was often dramatic, occasionally almost magical. A patient who had not slept for days except for intermittent nodding while sitting upright would report complete relief within two or three days after the drug was begun. Most patients noted some improvement within twenty-four hours, but in several instances the maximum result was not reached for a week or more. In many cases the benefit from digitalis was almost comparable to that from insulin in diabetic coma.

The length of time during which the drug was effective was not studied carefully in this series of cases, as many of the patients made only a few visits to the clinic. However, several patients have been followed for more than two years without any recurrence of paroxysmal dyspnea being noted. In other cases the symptoms have recurred despite digitalization.

The Effect of Digitalis on Dyspnea Brought on by Exertion.—Forty-three patients were studied and the findings are presented in table 2. Two patients reported that they had more dyspnea after

TABLE 1.—*The Effect of Digitalis on Paroxysmal Nocturnal Dyspnea*

Subject	Chief Diagnosis	Degree of Paroxysmal Dyspnea		Degree of Relief
		Before Digitalis	After Digitalis	
H. O.	Hypertension	+	0	Complete
D. S.	Hypertension	+	0	Complete
L. C.	Hypertension	++	0	Complete
M. G.	Hypertension	+++	0	Complete
A. C.	Hypertension	+	0	Complete
H. M.	Hypertension	++	0	Complete
J. P. W.	Hypertension	++	0	Complete
A. A.	Hypertension	++	+	Partial
W. T.	Hypertension	++	+++	Worse
H. Ma.	Hypertension	++	0	Complete
A. As.	Arteriosclerosis	++	+	Partial
R. O. E.	Arteriosclerosis	+	0	Complete
E. C.	Arteriosclerosis	+	0	Complete
P. N.	Arteriosclerosis	++	0	Complete
D. K.	Arteriosclerosis	+++	0	Complete
C. C.	Syphilitic aortitis	+++	0	Complete
F. D.	Syphilitic aortitis	++	0	Complete
S. R.	Mitral stenosis	+	0	Complete
A. C.	Cardiac hypertrophy	+	0	Complete

having digitalis. Twelve patients noticed no difference. Fourteen patients felt certain that they could perform the same exercise with less discomfort, and fifteen patients reported no dyspnea after digitalis. (The term "no dyspnea" does not mean that severe exercise would not have produced respiratory discomfort, but simply that the amount of exertion involved in the patient's daily life caused none.)

It is certain that the results were much less striking as regards dyspnea with exertion than as regards paroxysmal dyspnea. The latter symptom was relieved completely in approximately 85 per cent of the cases, whereas the former symptom was entirely abolished in only about 35 per cent. Although an additional third of the patients claimed to be benefited, it is difficult to evaluate their statements. Disappearance of a symptom is decidedly more convincing than mere improvement in it.

The Effect of Digitalis on the Ventilation Index.—As has been stated, it was our clinical impression that respiratory distress on exertion was often benefited by digitalis. However, the results were not

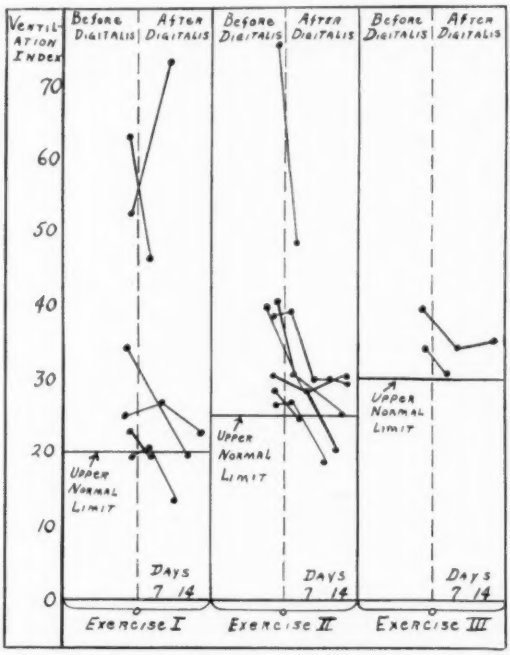
TABLE 2.—*The Effect of Digitalis on Dyspnea Brought on by Exertion*

Subject	Chief Diagnosis	Degree of Paroxysmal Dyspnea		Degree of Relief
		Before Digitalis	After Digitalis	
H. O.	Hypertension	+	+	None
D. S.	Hypertension	+	+	None
L. C.	Hypertension	++	0	Complete
M. G.	Hypertension	++	+	Partial
A. C.	Hypertension	+	0	Complete
H. M.	Hypertension	++	+	Partial
J. P. W.	Hypertension	+	0	Complete
A. A.	Hypertension	++	+	Partial
W. T.	Hypertension	++	+++	Worse
H. Ma.	Hypertension	++	+	Partial
A. As.	Arteriosclerosis	++	++	None
R. O. F.	Arteriosclerosis	++	+	Partial
E. C.	Arteriosclerosis	+++	++	Partial
P. N.	Arteriosclerosis	++	+	Partial
D. K.	Arteriosclerosis	++	0	Complete
C. C.	Syphilitic aortitis	++	++	None
F. D.	Syphilitic aortitis	+++	+	Partial
S. R.	Mitral stenosis	+	0	Complete
A. C.	Cardiac hypertrophy	++	+	Partial
A. H.	Hypertension	++	+	Partial
J. W. K.	Hypertension	++	0	Complete
J. R.	Hypertension	+	+	None
E. E.	Hypertension	+	+	None
W. N. B.	Hypertension	+	+	None
S. W.	Hypertension	++	++	None
B. S.	Hypertension	+	++	Worse
J. S.	Cardiac hypertrophy	++	0	Complete
L. C.	Hypertension	+	0	Complete
M. E. J.	Hypertension	++	+	Partial
M. C.	Hypertension	+	+	None
L. B.	Hypertension	++	++	None
D. T.	Hypertension	++	0	Complete
P. A. M.	Hypertension	++	0	Complete
J. V.	Arteriosclerosis	++	+	Partial
T. B. H.	Syphilitic aortitis	++	0	Complete
J. P.	Syphilitic aortitis	+	+	None
L. V.	Syphilitic aortitis	++	0	Complete
C. H.	Syphilitic aortitis	++	0	Complete
M. B.	Cardiac hypertrophy	++	+	Partial
W. K.	Chronic bronchitis	++	+	Partial
R. L.	Asthma	+	+	None
M. L. S.	Cardiac hypertrophy	+	0	Complete
J. A.	Hypertension	++	0	Complete

nearly so striking in this instance as they were in regard to paroxysmal nocturnal dyspnea, and even though we attempted to be very conservative in our reports, and to make allowance for the enthusiasm which many patients have over any new therapeutic measure, it was believed that the observations of the clinical states did not justify any definite

conclusions as to the value of the drug in these relatively early cases. For this reason an attempt was made to study the matter more exactly by means of the vital capacity, the ventilation per square meter and the ventilation index.

Observations on eight cases are shown in the accompanying chart. None of these patients had edema at the time they were studied, and none had even had more than the slightest pitting. Four of them had had paroxysmal dyspnea before digitalis was administered, and in three



It can be seen that the ventilation index was usually less after digitalis had been given. In several instances the diminution did not come until the patient had been taking the drug for several days. In only one subject was there a marked increase in the ventilation index after digitalis had been administered.

of the four this symptom disappeared soon after the drug was given. The fourth patient (W. T.) was not improved. All eight patients had dyspnea on exertion and four of them believed themselves much better in this regard after digitalis. Three of the others thought that their discomfort with exertion was less but did not seem certain. The eighth patient (W. T.) said that he was more short of breath on walking after digitalis and seemed to be so when he performed the test.

In the twenty-five determinations of the ventilation index after digitalis had been administered, a large reduction was observed thirteen times, a slight reduction six times, a slight increase (usually very slight) five times and a marked increase once (W. T.). Seven of the eight patients had, on the average, a lower ventilation index after the drug. In two patients, tests done after digitalis had been administered for two or three days only showed no change, but later tests showed a well marked decrease in the ventilation index.

The objection might be raised that since the observations after digitalis were made subsequent to those before the drug, the lower values were due not to the drug but to the fact that the patient had become used to the test and better trained to the exercise. This objection is not valid because almost every person is "trained" to climb stairs and also because it was shown in the previous paper of the series (Harrison, Turley, Jones and Calhoun [1930]) that initial values are not higher than those obtained on subsequent tests.

It is of some interest to note that before digitalis was given, the ventilation index was above the upper normal limit for the corresponding exercise in every patient (R. O. E. had a ventilation index of 19.9 for exercise I, the upper normal limit being 20; but for exercise II, his ventilation index was 26.5, the upper normal limit being 25.0). After digitalis, four of the eight patients had ventilation indexes at or below the upper normal limit, although only one of these (R. O. E.) was as low as the normal average.

COMMENT

Since both subjective and objective data were in agreement, the conclusion seems justified that digitalis is usually of value in patients with regular cardiac rhythm suffering from paroxysmal nocturnal dyspnea or from dyspnea on exertion (provided, of course, that the dyspnea is due to disease of the heart). The number of our patients with rheumatic heart disease was too small to justify generalizations in regard to this condition, but patients with hypertensive, arteriosclerotic and syphilitic heart disease were usually benefited. So far as we know, the present data constitute the first objective demonstration of the value of digitalis in benefiting the dyspnea of patients with regular rhythm without frank congestive failure, although Cohn and Stewart (1924) have demonstrated objective effects of the drug in such patients with congestive failure.

The observations concerning the ventilation index seem to indicate that this method of study may be of some general use in evaluating therapeutic measures in patients with cardiac disease. Until the present time it has been easy to determine whether a given drug was of value in combating cardiac edema, because the urine volume could be measured

and the patient could be weighed. Methods of expressing dyspnea quantitatively have not been available and this probably explains the general confusion which, as has been pointed out, has existed in regard to the value of digitalis at an early stage when the patient has dyspnea only.

Although the data reported indicate clearly that digitalis is of value in patients with cardiac disease and regular rhythm, they do not throw any light on the mechanism whereby the drug produced improvement except so far as they demonstrate improvement without changes in heart rate and without diuresis.

Heymans and Heymans (1926) have demonstrated the existence of respiratory reflexes arising from the heart and aorta. Recently, Sutton and Lueth (1930) have shown that acute mechanical distention of the aorta and of the left ventricle produces paroxysmal dyspnea in the dog. It is possible that reflexes from the heart may play some rôle in the production of paroxysmal dyspnea in man. If cardiac dilatation per se can produce dyspnea, one would expect digitalis to have a very beneficial action. However, the fact that the drug has such an effect in striking degree can in no sense be regarded as proof that the dyspnea is due to dilatation. Further data along this line are needed.

SUMMARY

The effect of digitalis has been studied in forty-three patients with regular cardiac rhythm. Most of the patients had never had congestive failure. None of them had more than slight edema at the time they were studied and the majority had none. The following results were obtained:

1. Nineteen patients had paroxysmal nocturnal dyspnea (cardiac asthma). Sixteen of these persons were completely relieved of this symptom by digitalis, two patients were partially relieved and one was worse after the drug.

2. Forty-three patients had dyspnea brought on by exertion. Definite benefit was obtained in fifteen of these, apparent benefit in fourteen and no improvement in twelve, and two patients were worse after the drug.

3. In eight subjects the vital capacity, ventilation per square meter on standardized exercise and ventilation index were studied. Seven of the eight patients reported clinical improvement of some degree and in all of them measurements of ventilation also indicated improvement. One patient felt worse after digitalis, and objective study of the ventilation showed that he was worse.

As a result of this study, it is concluded that digitalis is of great benefit in patients with paroxysmal dyspnea and is of some value in many patients with dyspnea brought on by exertion.

ILLUSTRATIVE CASES

CASE 1.—H. O., the patient, a Negress, aged 41, complained of mild smothering spells on lying down, and of slight shortness of breath on exertion; her ankles occasionally were slightly swollen.

Physical examination revealed slight cardiac enlargement, the pulmonic second sound was exaggerated and there was a soft systolic murmur at the pulmonic area. The pulse was regular; the blood pressure was 148 systolic and 100 diastolic; the Wassermann reaction was negative. Teleoroentgenograms showed that the heart was at the upper limit of normal size.

She was put on potassium iodide, and two weeks later her dyspnea was unimproved. Digitalis was then given, 1 Gm. daily for two days and 0.1 Gm. daily thereafter. Four days later she reported no nocturnal dyspnea or orthopnea. Two weeks after this there was still no orthopnea and the patient believed that her dyspnea on exertion was better.

CASE 2.—D. S., the patient, a Negress, aged 39, complained of slight dyspnea on exertion for several months; for one month she had had mild paroxysms of dyspnea at night. There had never been any edema.

Physical examination revealed slight cardiac enlargement. The blood pressure was 162 systolic and 100 diastolic. The Wassermann reaction was negative.

Digitalis was given; 1 Gm. daily for two days and 0.1 Gm. daily thereafter. A week later she reported that the nocturnal dyspnea had disappeared but that the dyspnea on exertion was unchanged. Since that time, two years ago, she has been free from nocturnal dyspnea and has taken digitalis at intervals with questionable effects on her dyspnea on exertion.

CASE 3.—L. C., an obese Negress, aged 43, complained of dyspnea and palpitation on the slightest exertion. These symptoms had been becoming progressively worse for seven months. She was unable to walk across the room without stopping to rest. For several weeks she had been forced to sit up to breathe at night, and she now was unable to sleep in bed even with three pillows. She would "doze" for a few minutes and then be awakened by dyspnea. During the last few days her ankles had been slightly swollen at night. She dated all of her symptoms from an attack of migratory polyarthritis. The heart was slightly enlarged, the point of maximal impulse being 1 cm. outside the midclavicular line. The rate was 104. There was a loud blowing apical systolic murmur, and "tic-tac" quality of sounds. The blood pressure was 172 systolic and 100 diastolic. No râles were heard in the lungs. There was no edema.

She was given digitalis; 1.8 Gm. in four days and 0.1 Gm. daily thereafter. She stated, a week later, that her nocturnal dyspnea was completely relieved and that she was able to walk at a normal pace without dyspnea. After six weeks, digitalis was stopped. Two months later she complained of dyspnea with very slight exertion. The drug was readministered and she again improved. In the past two years digitalis has been stopped seven times. On each occasion her dyspnea on exertion has become worse within a few weeks and on one instance nocturnal dyspnea reappeared one month after the drug was discontinued. In each instance there has been a rapid improvement in dyspnea following redigitalization.

CASE 4.—M. G., the patient, a Negress, aged 37, had had increasing dyspnea on exertion for one year and severe paroxysms of dyspnea and cough at night for five weeks. There had never been any edema.

Physical examination revealed an obese woman with severe orthopnea. The point of maximal cardiac impulse was in the sixth interspace, 4 cm. outside of the midclavicular line. All the sounds were exaggerated; the heart was overactive; there was a double apical gallop. The aortic second sound was accentuated and the pulmonic second sound more so. There was a loud high-pitched musical systolic murmur. The blood pressure was 160 systolic and 88 diastolic. The lungs were clear. The liver was not felt; there was the slightest pitting edema. The Wassermann reaction was "anticomplementary." The electrocardiogram showed sino-auricular rhythm. Teleoroentgenograms revealed moderate cardiac enlargement and dilatation of the aortic arch.

The patient was given 16 cc. of tincture of digitalis immediately, 4 cc. the following day and 25 drops daily thereafter. Five days later she reported that she had slept better the first night and had had no nocturnal dyspnea since then; her dyspnea on exertion was much improved.

For the past two years she has received digitalis most of the time. She has had one frank attack of congestive failure with edema; otherwise she has done fairly well.

CASE 5.—W. T., the patient, a Negro, aged 52, complained of progressive dyspnea on exertion for two months, and of severe paroxysms of nocturnal dyspnea for five weeks. At first he would only be awakened once each night but more recently the paroxysms had occurred whenever he went to sleep, and he had to sit up all night.

Examination revealed orthopnea, marked cardiac enlargement, a gallop rhythm, a faint apical systolic murmur, general arteriosclerosis and tenderness in the liver region. The blood pressure was 170 systolic and 130 diastolic. There was no edema. He was given digitalis, 1 Gm. immediately, 0.5 Gm. the following day and 0.2 Gm. daily thereafter. Nine days later he said that he had felt a little better for the first two days but that he was now worse than before; he was having severe paroxysmal dyspnea, and his dyspnea on exertion was worse. There was slight pitting edema.

CASE 6.—R. O. E., the patient, a white man, aged 55, had had dyspnea on exertion since influenza a year previously. During the past month this had increased, and he had been unable to carry on his usual work as construction superintendent. In the past three weeks he had had four attacks of nocturnal dyspnea, and had also noted substernal pressure brought on by exertion and relieved by rest. The heart was slightly enlarged, the point of maximal impulse being 2 cm. outside the midclavicular line. The rate was 80. There were occasional premature beats; there were no murmurs. The arteries were moderately thickened. The blood pressure was 115 systolic and 70 diastolic. Electrocardiograms showed a left ventricular preponderance. He was given digitalis, 1.8 Gm. in three days and 0.2 Gm. daily thereafter. Four days later he reported that his dyspnea on exertion was "possibly a little better" and that he had had no paroxysms of dyspnea. After taking digitalis for two weeks he said that was much better; he could walk further and faster and continued to be free from nocturnal dyspnea.

CASE 7.—A. H., the patient, a Negress, aged 53, had noticed dyspnea for one month on climbing stairs, and for the last week on less exertion. There had been no paroxysmal nocturnal dyspnea, but for the past few weeks she had had to sleep on two pillows. She had never had edema. The pulse rate was 96; about every fifth beat was premature. The point of maximal cardiac impulse was very forceful in the fifth interspace about 14 cm. from the midsternal line. The mitral first sound was normal in quality. The pulmonic second sound was slightly

accentuated and the aortic second sound was markedly so; there was a presystolic gallop at the apex and a soft apical systolic murmur. The blood pressure was 186 systolic and 138 diastolic. There were no râles in the lungs; the liver was not felt and there was no edema.

She was given 1.6 Gm. of digitalis in four days and then 0.2 Gm. daily. A week later she was seen again and complained of anorexia and nausea but no vomiting. She stated that her dyspnea was very much better. The point of maximal impulse was 12 cm. from the midsternal line; the gallop rhythm and extrasystoles had disappeared. The blood pressure was 220 systolic and 140 diastolic. The patient did not return to the clinic again.

Case 8.—J. W. K., the patient, a Negro, aged 34, had been short of breath on walking slowly uphill, for thirteen months; he had been a little worse recently. He had had no dyspnea when walking on the level and no paroxysmal dyspnea or edema.

Physical examination revealed a slightly enlarged heart, as shown both by percussion and roentgenography. The aortic second sound was ringing; a very faint diastolic murmur was heard along the left sternal border. The blood pressure was 170 systolic and 100 diastolic. Repeated Wassermann tests of the blood were negative. The patient was given digitalis, 1.8 Gm. in three days and then 0.2 Gm. daily. Two weeks later he reported that the dyspnea was less severe. At the end of another month he was still improved and had dyspnea only when running.

Case 9.—J. R., the patient, a Negro, aged 57, had numerous complaints referable to various systems. For an indefinite period he had had dyspnea on exertion but no paroxysmal dyspnea or edema. The only positive findings were arteriosclerosis, a blood pressure of 180 systolic and 120 diastolic, a pulse rate of 100 and a slight cardiac enlargement. During the two years in which he was followed he was thoroughly digitalized twice. On neither occasion could he report an improvement in his dyspnea.

Case 10.—J. S., the patient, had had increasing dyspnea on slight exertion for a month. He also had had a chronic cough for an indefinite period. He had had no nocturnal dyspnea or edema.

Examination revealed marked cardiac enlargement, a blood pressure of 108 systolic and 80 diastolic, with marked alternation and very loud heart sounds. The electrocardiograms showed notching of the QRS complex, inverted T 1 and T 2 and a left ventricular preponderance. Following digitalization—1.2 Gm. in three days, followed by 0.2 Gm. daily—he reported that his shortness of breath was very much better. Three months later digitalis was stopped and within a month he again noted dyspnea on slight exertion. He was redigitalized, and ten days later said that he could perform ordinary activities with comfort and was dyspneic only with severe exertion.

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MECHANISMS OF THE CONTRACTION AND EVACUATION OF THE GALLBLADDER *

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The factors concerned in the contraction and evacuation of the gallbladder have been greatly clarified by Ivy and his collaborators,[1] who have shown that the introduction of acid or of digested fat into the duodenum liberates a hormone, named by them "cholecystokinin," which causes an active contraction of the viscus. Their work indicates that this liberation of cholecystokinin is one of the principal mechanisms by which evacuation of the gallbladder is effected. In view of their reports, an evaluation of other possible mechanisms is of importance.

REFLEX AND DIRECT STIMULATION OF THE EXTRINSIC NERVES

The literature on the extrinsic nerves of the gallbladder was reviewed in 1924 by Mann,[2] who was led to conclude that the vagus is mainly motor and the splanchnic mainly inhibitory. Experimental work up to this time had been largely concerned with stimulation of the nerves under anesthesia and by means of drugs, but several investigators have subsequently used more physiologic methods. Whitaker [3] filled the gallbladders of dogs with iodized oil and placed shielded electrodes on the vagus; stimulation of the vagus some time after recovery from the anesthesia did not result in any change in the shadow of the gallbladder. He also found that the gallbladder reacted normally to a meal after section of both the vagus and the splanchnic. To study the effects of stimulation of the splanchnic in human beings he injected epinephrine, but observed no response. Copher and Kodama [4] visualized the gallbladders of dogs by injection of dye and were unable to find any definite evidence of control by the vagus or

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1. Ivy, A. C., and Oldberg, E.: Am. J. Physiol. **86**:599, 1928. Lueth, H. C.: Ivy, A. C., and Kloster, G.: Am. J. Physiol. **91**:329, 1929. Ivy, A. C.: Proc. Internat. Assemb. Inter-State Post-Grad. M. A., North America (1929) **5**:378, 1930.

2. Mann, F. C.: Physiol. Rev. **4**:251, 1924.

3. Whitaker, L. R.: Am. J. Physiol. **78**:411, 1926.

4. Copher and Kodama: Unpublished; quoted by Graham et al (footnote 14).

splanchnic. Boyden [5] found that epinephrine injected intravenously into cats produced a diminution of the size of the shadow of the gallbladder. Burget,[6] however, expressed the belief that this is due to relaxation of the distal end of the common bile duct rather than to contraction of the gallbladder. Birch and Boyden [7] found changes in the shape of the gallbladder occurring reflexly on electrical stimulation of the stomach and large intestine in unanesthetized animals. Sosman, Whitaker and Edson [8] observed no effect on the human gallbladder from the sight, smell, or taste of food, nor did they find any consistent effect as a result of subcutaneous injections of atropine, physostigmine, pilocarpine or epinephrine in human beings. Whitaker [9] stated that letting a hungry dog take food into its mouth is without effect on the shadow of the gallbladder. Boyden and Birch [10] found that "smelling of food has no effect upon the gallbladder," although later Boyden [11] reported that when patients are allowed to smell bacon there is a momentary discharge of bile. According to Elman and McMaster,[12] who worked on dogs, the taking of food is immediately followed in most cases by a brief increase in pressure in the gallbladder and a decrease in the resistance offered by the common bile duct to the outflow of bile.

EFFECTS OF SHAM FEEDING ON EVACUATION OF THE GALLBLADDER

In view of the contradictory reports in the literature on the action of the extrinsic nerves, it was felt that further experimental work was indicated. Sham feeding suggested itself as a method of attack on this problem, since it is well known that sham feeding reflexly stimulates the vagus, markedly increasing the secretion of gastric juice and to a slight extent the secretion of pancreatic juice, as well as influencing the motility of the gastro-intestinal tract. A review of the literature failed to show any report on the use of sham feeding in this connection. Accordingly, four dogs were prepared with esophageal and gastric fistulas. The gallbladders of these animals were visualized, and they were allowed to drink egg yolk or to eat chopped meat for

5. Boyden, E. A.: Anat. Rec. **33**:201, 1926.

6. Burget, G. E.: Am. J. Physiol. **81**:422, 1927.

7. Birch, C. L., and Boyden, E. A.: Am. J. Physiol. **92**:301, 1930.

8. Sosman, M. C.; Whitaker, L. R., and Edson, P. J.: Am. J. Roentgenol. **14**:495, 1925.

9. Whitaker, L. R.: The Mechanism of the Gallbladder and Its Relation to Cholelithiasis, J. A. M. A. **88**:1542 (May 14) 1927. Krause, W. F., and Whitaker, L. R.: Am. J. Physiol. **87**:172, 1928.

10. Boyden, E. A., and Birch, C. L.: Proc. Soc. Exper. Biol. & Med. **24**:827, 1927.

11. Boyden, E. A.: Proc. Soc. Exper. Biol. & Med. **25**:99, 1927.

12. Elman, R., and McMaster, P. D.: J. Exper. Med. **44**:151, 1926.

from one-half to one hour. In three of the animals the gastric juice was withdrawn from the stomach every five minutes during the period of sham feeding; in the fourth dog it was not removed, nor did leakage occur through the gastric fistula. Six tests were made on these four animals, and in no instance did sham feeding cause any apparent change in the size or density of the shadow of the gallbladder. In each case the gallbladder evacuated completely after the introduction of egg yolk into the stomach through the gastric fistula. The dogs were all in good condition and hungry at the time of the experiments.

EFFECTS OF PSYCHIC STIMULI ON EVACUATION OF THE GALLBLADDER IN HUMAN BEINGS

To test the effects of psychic stimuli on the evacuation of the gallbladder in human beings, two healthy male medical students were given intravenous injections of dye and fasted for more than forty-eight hours. During this time they were repeatedly subjected to the sight and smell of food which others were eating.[13] In neither case was there evidence of emptying of the gallbladder as a result of the psychic stimuli.

EFFECTS OF DIRECT STIMULATION OF THE VAGUS AND SPLANCHNIC NERVE ON EVACUATION OF THE GALLBLADDER

In view of the negative results of sham feeding and of psychic stimuli, it was decided to repeat the experiments of previous workers in the direct stimulation of the vagus and splanchnic nerve. In three dogs shielded electrodes were placed on the peripheral end of the right vagus, just above the diaphragm; the left vagus was similarly treated in one dog. Ether anesthesia and aseptic technic were used. At the same time the gallbladders of these animals were filled with iodized or brominized oil. Stimulation of the peripheral vagus with a tetanizing current on the following day for from one-half to one hour caused audible borborygmi but did not result in any expulsion of oil into the duodenum. Similar stimulation of the right splanchnic nerve in one dog whose gallbladder was filled with iodized oil was likewise without effect. All the animals responded to a fat meal or to the intravenous injection of cholecystokinin by the expulsion of considerable amounts of the radiopaque oil from the gallbladder. Stimulation of the

13. The results of these experiments on human beings, as well as all the other human experiments, are reported by the courtesy of Dr. James T. Case, Professor of Roentgenology, Northwestern University Medical School, under whose auspices they were performed, and of Dr. E. R. Crowder, Fellow in Roentgenology, who assisted in the human experiments.

splanchnic in one human subject was attempted by the subcutaneous injection of 0.5 cc. of epinephrine; there was no resulting change in the shadow of the gallbladder, although emptying occurred following a fat meal. In a personal communication, Dr. Case [13] stated that he had had consistently negative results in fifteen such experiments, although he had injected as much as 1 cc. of epinephrine.

Thus all attempts to induce contraction of the gallbladder by means of artificial direct stimulation or normal reflex stimulation of the vagus and splanchnic in human beings and dogs were unsuccessful, which agrees with the results obtained by the majority of previous workers. Sham feeding is the strongest normal type of reflex excitation of the digestive processes that are under the influence of the vagus. Since sham feeding in the dog and psychic stimuli in man do not affect the shadow of the gallbladder, it is probably not necessary for the patient who has been given the Graham test to avoid the sight or smell of food.

SPONTANEOUS EMPTYING

Graham and his associates [14] brought forth evidence pointing to spontaneous emptying, which they ascribed to a washing out of the bile in the gallbladder by freshly secreted bile from the liver. Whitaker [9] stated that he had observed in dogs spontaneous emptying of gallbladders filled with "light iodized oil," but offered no explanation for the phenomenon. Iodized poppy-seed oil 40 per cent, which had been used by many workers for filling the gallbladders of experimental animals, has a viscosity of 90 at 20 C. (water taken equal to 1), while the average viscosity of eight samples of the bile from dogs' gallbladders was found to be 1.8 at 38 C. (maximum 2.2, minimum 1.4). A much greater force would be necessary to empty the highly viscous iodized poppy-seed oil than to expel the bile in the gallbladder. Accordingly the gallbladders of seven dogs were filled with a radiopaque brominized oil having a viscosity of 5.3 at 38 C.; since the viscosity of this oil approaches so much more closely that of the bile of the gallbladder, normal conditions were more nearly approximated. In all seven dogs the gallbladders emptied spontaneously; in most cases they were more than half empty at the end of from eighteen to twenty-four hours. It was considered that the nonoccurrence of spontaneous emptying in gallbladders filled with iodized poppy-seed oil might have been due to the fact that the oil was too viscous to pass the sphincter of Oddi. Four dogs were prepared with cannulas in the intramural portion of

14. Graham, E. A.; Cole, W. H.; Copher, G. H., and Moore, S.: Diseases of the Gall Bladder and Bile Ducts, Philadelphia, Lea & Febiger, 1928.

the common bile duct and extending into the lumen of the duodenum, so that resistance in the intramural portion of the duct and in the sphincter would be eliminated. When the gallbladders of these animals were filled with iodized poppy-seed oil, spontaneous emptying took place comparable to that observed when the gallbladder was filled with a light brominized oil.

Spontaneous emptying of the human gallbladder after visualization by tetiothalein sodium has apparently not been observed. According to Sosman, Whitaker and Edson [8] and Krause and Whitaker,[9] even a meal

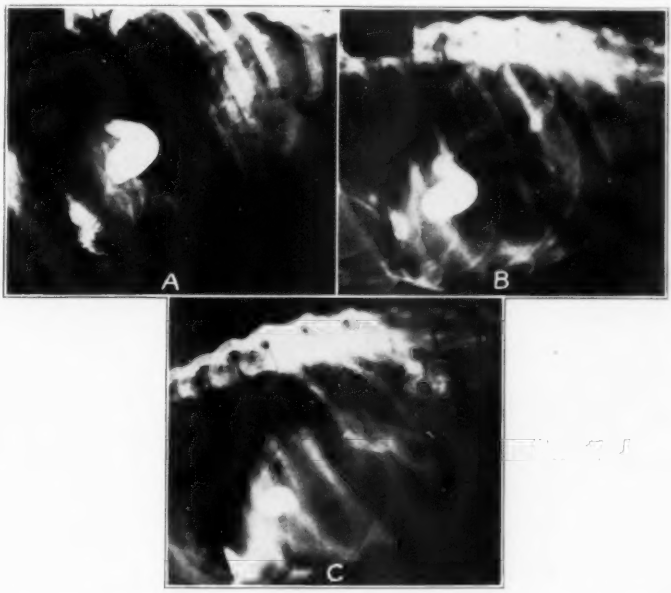

Fig. 1.—Gallbladder filled with brominized oil with viscosity of 5.3, showing spontaneous emptying. *A*, fifteen minutes after filling; *B*, six hours after filling; *C*, twenty hours after filling.

of carbohydrates has no effect on the shadow. Case [15] stated that a carbohydrate meal taken one or two hours after intravenous injection of the dye does not interfere with visualization. Four experiments were conducted which confirmed the foregoing reports. Spontaneous emptying in human beings was studied in two subjects, who had received the dye intravenously. Roentgenograms were made through-

15. Case, J. T.: Evaluation of Cholecystography, J. A. M. A. **92**:291 (Jan. 26) 1929.

out a period of fasting of fifty and fifty-two hours, respectively. In one of the subjects there was a slight decrease in the opacity of the gallbladder forty-eight hours after injection of the dye; in the other there was no evidence of emptying. In two cases in which carbohydrates alone were eaten following visualization of the gallbladder in human beings, the shadow definitely though slowly decreased in density, the change being distinctly appreciable within twenty-four hours. Lueth [16] showed that each peristaltic wave of the duodenum in anesthetized dogs is associated with a decrease in the resistance to the flow of bile into the intestine. Others ascribed the emptying of the gallbladder entirely to intestinal motility. The slow emptying of the human gallbladder when fat and protein are eliminated from the diet shows, however, that peristalsis in the duodenum is not the primary factor in the rapid emptying that occurs following a mixed meal. Spontaneous emptying of oil, as observed in the dog, may be a result of contractions that are secondary to the trauma caused by the injection of the oil, although in general any injury to the viscus tends to delay rather than to stimulate emptying. In human subjects the relatively long persistence of the shadow may conceivably be ascribed to a reabsorption and reconcentration of any expelled dye, facilitated by an empty gastro-intestinal tract.

COMMENT

The purpose of this study is not the evaluation of all of the factors that may cause minor changes in the tonus of the gallbladder or effect the expulsion of small amounts of bile; it is rather the determination of what mechanisms are responsible for the relatively complete emptying that indubitably occurs following a mixed meal. This has variously been ascribed to a reflex stimulation involving the extrinsic nerves, to duodenal motility with relaxation of the sphincter of Oddi, to the effects of respiratory movements and to elastic recoil of the distended viscus. More recently Ivy [1] has shown that the specific effect of digested fat is the liberation of a hormone which causes contraction of the musculature of the gallbladder and may produce almost complete emptying. Space does not permit a complete discussion of all of the theories that have been advanced to explain the evacuation of the gallbladder. Most workers are now agreed that it is largely effected by contraction of the smooth muscle in the wall of the viscus. The resistance offered by the intramural portion of the common bile duct undoubtedly plays a part, since it has been shown that the pressure necessary to eject bile through the duct may vary within wide limits.

16. Lueth, H. C.: Unpublished work.

and that bile usually enters the duodenum in spurts synchronous with the waves of peristalsis. That this is not a major factor is shown by the facts that, after section of the common bile duct, emptying occurs relatively slowly (Boyden and Birch [10]); that emptying is likewise slow when the diet is limited to carbohydrates, and that physostigmine, which increases peristalsis, and epinephrine, which relaxes the intestines, have no marked effect on the shadow of the gallbladder. Boyden [5] especially has brought forth evidence that the extrinsic nerves exercise some control over the motility of the gallbladder. His experiments with the intravenous injection of epinephrine may be regarded as unphysiologic, and in the hands of several workers epinephrine injected subcutaneously had been ineffective (Whitaker,[3] Sosman et al.,[8] Case [12]). He found that reflexes set up by electrical stimulation of the stomach or of the large intestine may cause changes in the shape of the gallbladder and the evacuation of small amounts of bile, but that such reflexes do not cause massive emptying similar to that provoked by a meal containing fat or protein. The extrinsic nerves seem to play only a minor rôle, if any, in the normal functioning of the organ. The washing out of the contents of the gallbladder with fresh bile from the liver, as suggested by Graham, in conjunction with the part played by duodenal motility, may result in the gradual evacuation of the contents of the gallbladder over a period of many hours, in the absence of a specific stimulus. It is possible that the liberation of cholecystokinin by the action of fat in the stomach may assist somewhat in evacuation (Drewyer and Ivy [17]). The present study, however, indicates that the liberation of cholecystokinin from the upper intestine by the action of fat or of acid is chiefly responsible for the rapid and complete emptying of the gallbladder in response to a mixed meal, duodenal motility facilitating the process.

CONCLUSIONS

1. Sham feeding and direct stimulation of the vagus and splanchnic nerve in dogs, and psychic stimuli and the injection of epinephrine in human beings have not been found to have any effect on the motility of the gallbladder.

2. The gallbladders of dogs when filled with brominized oil that is less than three times as viscous as bile empty about one half of the oil spontaneously in from eighteen to twenty-four hours.

3. The gallbladders of dogs when filled with iodized oil of the usual relatively high viscosity empty about one-half spontaneously in from

17. Drewyer, G. E., and Ivy, A. C.: Proc. Soc. Exper. Biol. & Med. **27**:186, 1929.

twelve to twenty-four hours when the resistance of the intramural portion of the common bile duct is eliminated.

4. In fasting human subjects little tendency toward spontaneous emptying of the gallbladder is observed.

5. In human subjects on a carbohydrate diet there is a tendency toward emptying of the gallbladder over a period of from twenty-four to forty-eight hours.

6. It is concluded that the liberation of cholecystokinin by the action of fat or of acid in the intestine is the major factor concerned in the contraction and evacuation of the gallbladder that follow a mixed meal. Duodenal motility facilitates this process.

PROPHYLAXIS OF POSTOPERATIVE PNEUMONIA BY ORAL HYGIENE

A PRELIMINARY REPORT *

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For the past two decades, serious consideration has been given to the etiology and prevention of postoperative pneumonia. In a large majority of the well organized hospitals, suggestions made by such men as Whipple,[1] Elwyn [2] and Henderson [3] are now incorporated as a matter of routine. These suggestions include:

1. The better protection of the patient from chills and drafts before, during and after operation and in his journey to and from the operating room.
2. The use for abdominal operation of bandages of a type that will aid in relieving the pain of breathing and permit deeper inhalation.
3. The use of opiates for a few days post operation to facilitate breathing by elimination of pain.
4. The inhalation of carbon dioxide and oxygen at the termination of general anesthesia, for ventilating and removing the anesthetic from the lungs to restore normal breathing.
5. The postponement of operations in the presence of active or recent disturbances of the upper respiratory tract.
6. The choice of anesthesia and its administration by a trained personnel.

Among other factors in the causation of postoperative pneumonia are:

1. The site of operation.
2. The presence of latent pulmonary disease.
3. The aspiration of septic material from the mouth.

Among these causes and factors, the aspiration of septic material from the mouth during anesthesia probably contributes the largest share of potential danger to the patient; indeed, Featherstone [4] quoted Prof.

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* Submitted for publication, March 28, 1931.
* From the Dental Service, Lenox Hill Hospital.
* Read before the New York Academy of Medicine, Section of Surgery and Rhinology, Dec. 6, 1930.

1. Whipple, A. O.: Post-Operative Pneumonitis, Surg., Gynec. & Obst. **26**:29 (Jan.) 1918.

2. Elwyn, Herman: Post-Operative Pneumonia, J. A. M. A. **79**:2154 (Dec. 23) 1922; **82**:384 (Feb. 2) 1924.

3. Henderson, Yandell: Acapnia as a Factor in Post-Operative Shock, Atelectasis and Pneumonia, J. A. M. A. **95**:572 (Aug. 23) 1930.

4. Featherstone, Henry: An Inquiry into the Causation of Post-Operative Pneumonia, Brit. J. Surg. **12**:487 (Jan.) 1925.

J. Shaw Dunn of the chair of pathology at Birmingham (England) in saying that aspiration pneumonia is the commonest form of postoperative pneumonia. Obviously, it is not possible to prevent entirely the aspiration, but it seems that a reduction of its septic and filthy properties might be feasible and of extreme value. Not only because little, if any, work had been done along these lines, but because this particular field of prophylaxis lay within the province of the dentist, I was moved several years ago to suggest to the attending surgeons of the Lenox Hill Hospital that we strive to eliminate the infectious condition of the mouth before operation, and thus test the validity of this hypothesis. Although the proposal met with immediate cooperation and aid, our procedure at the outset was, of necessity, makeshift, for the dental department was not sufficiently manned for the undertaking. However, as an initial step in the preoperative oral care of surgical patients, we made a brief trial in 1925, selecting the medical pneumonia season of February and March. We subjected the patients in one of the active surgical services to the new routine and used those in the other service as controls.

I regret to say that the result of six weeks' trial was discouraging, for a patient in the service receiving oral care developed postoperative pneumonia on the last day of the experimental period. But the fact that the patient had had a hernioplasty performed under a local anesthetic did much to mitigate a natural disappointment, and we decided to continue the experiment at a later date, for the intensive preoperative oral care of the surgical patients, in addition to the care of all the other ward patients, for more than a limited period, proved too severe a physical strain on the dental intern. Therefore, continuing with the February and March seasons of the following and succeeding years, we alternated each year from one surgical service to another, and gave the patients during that time complete preoperative oral care. Then, early in 1928, on the appointment of a dental prophylactic nurse to the staff to assist the intern, we began at the end of February of that year with a full and complete dental routine for the preliminary care of all the operative patients in the surgical and genito-urinary services. No other changes were inaugurated in the treatment or handling of surgical patients. The usual care was continued, with only the addition of the intensive oral care by the dental department.

TECHNIC

Adhering to the general fact that patients with nonemergency cases are admitted to the hospital for observation from two to four days prior to operation, the dental department contrives to do its work during that period. This can, and is, done without interfering with the patients' usual preoperative surgical routine of examinations, laboratory tests and observation.

As soon as possible after admission to the wards, the patient is sent to the dental room, which is situated near the surgical wards. First, the gums and teeth are thoroughly swabbed by the dental hygienist with a solution consisting of:

Zinc chloride	15 parts
Aqua destillata	10 parts
Iodine crystals	25 parts
Glycerin	50 parts

After the swabbing, the teeth are thoroughly scaled and polished, and the condition of the mouth is charted, on a separate dental sheet of a distinguishing color, as to carious teeth, teeth to be extracted, missing teeth, condition of the soft parts and the presence of crowns and bridges. The patient is also instructed in the proper use of a toothbrush, and, if without, he is presented with a good, serviceable one. This toothbrush is not the usual clinic type, with bamboo handle, but has a good bone handle with seven pairs of double-row bristles.

The patient then returns to the ward, where the medical nurse sees that he uses hourly a mouth wash consisting of a 2 per cent formaldehyde solution—a teaspoonful to one-half glass of water. In the event of infected roots or teeth, the dental intern immediately begins to extract one at a time, at intervals of twenty-four hours, and then only if there has been no unfavorable reaction after the first or subsequent extractions. If any reaction, such as a rise of temperature, should occur post extraction, the intern is not permitted to continue until not only the subsidence of symptoms takes place, but also a consultation is held with the surgical staff as to the advisability of further extractions. Extractions are never done in the twenty-four hours immediately preceding the scheduled surgical operation.

On the second morning after admission, the patient's mouth is again swabbed with the solution used immediately after admission, and the formaldehyde mouth wash is used every hour. This daily swabbing and hourly mouth wash are continued up to the time the patient leaves the ward to go to the anesthesia room, where he gets the final swab and mouth wash.

This completes the technic incorporated for periods of about six weeks up to Feb. 26, 1928, when, with the appointment of a dental hygienist, we continued to give the preoperative oral care described through the entire year. Although the work is still being carried on, our report ends on Feb. 26, 1930, completing two years of intensive work. Unfortunately, this does not give us as large a number of patients as we should wish, as the figures are depleted by the large percentage of patients who did not go to operation as well as by the number of those who were transferred to other services. Emergency operations are also excluded from the report, but we hope to work out a rapid technic that may be used in such instances. The results on the 859 patients, however, show such a marked decrease in the cases of pneumonia that I feel justified in offering the report as it stands, and trust that in time we shall be able to base our findings on the same number of patients as do Whipple, Cleveland, Elwyn and others.

It is of value to study the figures given by Featherstone on the number of cases of postoperative pneumonia reported from various sources. Those cited prior to 1919 have been omitted from this report, but the

figures of the Lenox Hill Hospital have been added (table 1). The table given by Featherstone shows a low of 2.6 per cent and a high of 8.5 per cent, whereas the patients who have had preoperative oral care at the Lenox Hill Hospital show an incidence of 0.81 per cent of postoperative pneumonia.

It is also interesting to note (table 2) that in 1927, at the Lenox Hill Hospital, of 975 noncontrolled patients operated on, 25 developed post-

TABLE 1.—*Figures Given by Featherstone on the Number of Postoperative Pneumonias Reported from Various Sources, with Those of Lenox Hill Hospital Added*

Year		Patients Operated on	Pneumonias	Incidence, per Cent
1919	Cleveland	1,940	65	3.30
1918	Whipple	3,719	97	2.60
1921	Mandl	1,585	..	8.50
1922	Herb	1,534	76	5.00
1922	Elwyn	2,932	81	2.76
1924	Elwyn (General)	1,734	52	3.00
1924	Elwyn (Local)	399	11	2.70
	Lenox Hill Hospital	859	7	0.81

TABLE 2.—*Lenox Hill Hospital Figures: Incidence of Postoperative Pneumonia Before and After Establishment of Preoperative Oral Care*

Year	Patients Operated on			
	Without Preoperative Oral Care	With Preoperative Oral Care	Postoperative Pneumonias	Incidence per Cent
1927	975	...	25	2.5
1928	...	298	2	0.7—
1929	...	419	3	0.7

TABLE 3.—*Figures Given by New York City Board of Health Showing Rise in Number of Cases of Pneumonia Throughout the City*

Year	Cases of Pneumonia	Case Rate per 100,000 Population
1927	18,273	306
1928	21,079	350
1929	21,132	358*

* An increase of approximately 16 per cent.

operative pneumonia—an incidence of 2.5 per cent, which compares favorably with the current low reports to that date; also that, although no other measures were employed, the results during 1928 and 1929, up to Feb. 26, 1930, when the routine of oral care was strictly carried out, show an incidence of 0.7 per cent.

The question arises whether there was a decided drop throughout the city in medical pneumonias during those particular two years. An inquiry at the New York City Board of Health elicited the reply shown in table 3. This indicates a rise from 306 per hundred thousand of

population in 1927, to 358 per hundred thousand, in the greater city. This is a rise of approximately 16 per cent throughout Greater New York. During this same period, the patients at the Lenox Hill Hospital who received preoperative oral care showed a decrease in the incidence of postoperative pneumonia: only 5 of 717 patients who received preoperative oral care developed postoperative pneumonia, as compared with 25 of 975 patients who did not receive such care. This represents a reduction of from 2.5 per cent to 0.7 per cent, or a little more than two thirds.

Table 4 indicates the regions of the body operated on, the numbers of operations performed and the numbers of postoperative pneumonias with the incidence per cent. Of the 468 abdominal operations, 4 led

TABLE 4.—*Regions of Body Operated on, Numbers of Postoperative Pneumonias and Incidence per Cent*

Region Operated on	Operations	Postoperative Pneumonias	Incidence per Cent
Abdomen	468	4	0.86
Rectum	146	..	....
Genito-urinary organs	42	2	4.80
Head and neck	51	1	2.0
Thorax	35	..	....
Extremities	117	..	....
Total	859	7	0.81

TABLE 5.—*Types of Anesthesias, Number of Postoperative Pneumonias and Incidence per Cent*

Anesthesias	Postoperative Pneumonias	Incidence, per Cent
General, 668	3	0.5
Local, 149	3	2.0
Colonic, 6	1	16.6
Spinal, 36	..	....
Total, 859	7	0.81

to postoperative pneumonia, or 0.86 per cent. Three of these were operations for hernias, and the fourth was performed on a young boy who underwent two laparotomies within a short time; the pneumonia developed after the second operation. The two in the genito-urinary service were prostatectomies performed on old men. The one patient in the head and neck division was under colonic anesthesia for a long period—over five hours. He underwent the removal of a carcinoma of the cheek, the cervical glands were dissected, and a plastic operation was performed.

Table 5 indicates the various types of anesthesias employed. The figures for patients operated on under general anesthesia are most gratifying, with an incidence per cent of only 0.5. Of the three patients operated on under local anesthesia, with an incidence per cent of 2, it

was disclosed, on examination of the case histories, that two had had hernioplasties and the third a prostatectomy. The high percentage for those operated on under colonic anesthesia is due, possibly, to the fact that we have so few to report on. The patient who developed the postoperative pneumonia was the one mentioned as having had the long experience in the operating room.

All of these records of patients suffering from postoperative pneumonia were taken from the history charts, and the diagnoses were always made by the surgical and medical staffs. After the routine preoperative oral care was completed, the dental department had no further contact with the patients. Reports were received from the record room.

SUMMARY

For the successful execution of a work of this nature, it is essential for the dental department to have the full cooperation of both the surgical staff and the superintendent of nurses. At the Lenox Hill Hospital, I received encouragement and aid from these sources.

By the use of this technic, which has been developed over the past five or six years, we believe that the mouth can be put into a reasonably clean, hygienic state before the operation is performed. At various times, suggestions for milder methods have been presented by those cognizant of the work, but at each substitution the results proved to be less beneficial to the patient, and we have always reverted to the routine described.

This preliminary report on 859 surgical patients who were given definite preoperative oral care indicates a measurable drop in postoperative pneumonias. In the figures submitted, this drop amounts to two-thirds, and as nothing was changed and no other measures were taken, it seems to point out the practical value of a standard preoperative oral routine. This routine can be established in any general hospital with comparatively small expenditure, but it requires constant cooperation and surveillance.

26 East Thirty-Sixth Street.

AZOTEMIA WITH NORMAL KIDNEYS FOUND POST MORTEM

POSSIBLE CAUSE: LOW BLOOD PRESSURE AFTER OPERATION *

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The physiologic processes of the kidney require certain constant factors. The tissue of the kidney must be normal if it is to concentrate the sodium chloride of the blood and maintain it at a constant level and if it is to maintain the nitrogenous factors of the blood at a normal level. The blood pressure must be within certain normal limits if the kidney is to secrete properly fluid and other products in solution. If the blood pressure is to be maintained at a certain level, the heart or propulsive force must be adequate, and the blood vessels must have a certain tone and consistency. The failure of any of these functions individually results in the failure of the general excretory functions of the kidney as a whole.

Physicians are familiar with the pictures that result from damage to the arteries and other blood vessels of the kidneys and those that result from damage to the secretory cells of the kidney. Ambard, Volhard and Fahr, Floyd and others have demonstrated the relation of this type of damage to hypertension, cardiac hypertrophy and damage of the tissues, and azotemia. The converse relation of hypertension or so-called malignant hypertension without much demonstrable arterial damage to failure of the function of the kidney and heart failure is also well known. During recent years it has been demonstrated by Atchley and his school that a condition similar to the well known "surgical shock," with a sudden fall in the blood pressure and death, occurs frequently. These workers pointed out the fact that such cases of vascular failure were frequently erroneously called "heart failure" and that even in the presence of signs of edema of the lungs, the treatment accorded in cases of surgical shock—the intravenous administration of physiologic solution of sodium chloride, dextrose and blood—was effective in saving life. However, the cases described by Atchley showed evidences of circulatory failure in the lungs and elsewhere and did not show any considerable rise in the nitrogenous components of the blood. Lastly, Floyd has described cases of mechanical failure of the kidneys due to sudden, almost complete destruction of the kidney by embolic abscesses or infarcts.

* Submitted for publication, March 2, 1931.

The case report in this article is demonstrative of a condition a description of which I have not been able to find in the literature. The case was one of acute renal failure with anuria and resulting fatal azotemia, clinically similar to that seen in scarlet fever and poisoning with corrosive mercuric chloride, but differing greatly from it in certain respects. The anuria was followed much more promptly by death than in cases due to scarlet fever or poisoning with mercury. The nitrogenous factors in the blood rose much faster than in the other conditions. The blood pressure in this case was uniformly very low. At autopsy, the renal, hepatic and cardiac tissues were found to be normal, whereas damage to one or all of these tissues is seen at autopsies performed in cases of scarlet fever or poisoning with mercury.

REPORT OF CASE

History.—R. H., a white man, aged 35 years, married, a sales executive, was seen by Dr. Leonard Bacon early in the afternoon of Oct. 21, 1930. He had driven to New Haven from Boston on October 20, and had eaten a large and rather rich evening meal. He had gone to bed on this evening feeling well, but was awakened from sleep at 4 a. m., October 21, by a severe abdominal pain. By the time that Dr. Bacon arrived, at 1:30 p. m., October 21, he had vomited once, with partial relief from pain. There were no other symptoms.

Examination.—Physical examination made at this time showed a temperature of 101 F., with a relatively slow pulse rate, about 84. There was abdominal pain and tenderness in the hypogastrium near the midline, but there was no pain or tenderness near McBurney's point. The rest of the physical examination gave normal results. The patient was seen later that afternoon, when it was found that the pain had abated somewhat and that the temperature was higher—104 F.—and the pulse rate, 104. He had not vomited in the interim. At this examination the urine was clear and contained no albumin.

The following morning, the patient was seen again; the temperature had subsided to 101.6 F., and the pulse rate was slow, 84. However, there had been no vomiting. The character and position of the pain had not changed, and the results of physical examination were the same. During the afternoon of this day, more tenderness and pain developed, and there was some localized spasm of the lower portion of the right rectus muscle. The lungs were still clear; the temperature was 104 F., and the pulse rate, 104. A blood count made at this time showed: white blood cells, 15,000; polymorphonuclears, 92 per cent. He was sent to Grace Hospital immediately with the diagnosis of acute appendicitis and was admitted there with a temperature of 101.8 F. and a pulse rate of 90. Examination of the urine made at that time showed a high specific gravity and a trace of albumin. There were a few hyaline and granular casts and an occasional red blood cell.

Operation.—Operation was performed immediately and, with the patient under ethylene anesthesia, a girdiron incision was made over McBurney's point. A mass of inflammatory tissue was felt toward Poupart's ligament. The rest of the peritoneum was found to be in good condition. As the mass could not be delivered easily, the incision was enlarged downward. A gush of seropus followed the insertion of the exploring finger. The omentum was drawn away with the inflamed mass and delivered through the wound. It was indurated and inflamed

and obviously had acted as an involucrum surrounding the gangrenous appendix. The inflamed portion of the omentum was clamped and resected. The appendix was clamped and removed together with the mesentery. There were slight hemorrhage and slight handling of the intestines. About one-fourth inch (6.35 mm.) from the cecum the appendix did not show gangrene, and the stump was tied off at this point. The clamped portions were ligated, and the intestines and omentum were dropped back into the abdominal cavity. Three large cigaret drains were inserted, one into the pelvis and two others to the outside of the cecum and ascending colon. Two silkworm gut sutures were passed through the whole abdominal wall and a cigaret drain and gauze pack were inserted along the edges of the wound to act as a plug and to guard against herniation of the intestinal coils through the considerable opening in the abdomen. The patient was taken from the operating table in good condition.

Pathologic Report.—The pathologic specimen was a gangrenous appendix which was very thin-walled, collapsed and discolored. There was also some indurated and inflamed fat tissue. Under microscopic scrutiny only a small part of the tissue could be identified as appendix because of the marked gangrene.

Course.—The patient did exceedingly well for the first five days after the operation. The temperature immediately fell to normal and remained so through the course. The pulse was consistently slow and for five days was of good quality. The respiratory rate was consistently 22 throughout the course. The patient took fluids exceedingly well and passed copious urine. There was some distention of the abdomen but, considering the magnitude of the pathologic process, the distention was moderate. Flatus was passed early, and several partially formed stools were passed also. There was no postoperative vomiting.

The condition of the patient became slightly worse during the afternoon of the fifth day, but was not alarming, and he had a fairly restful night. Beginning at noon of the sixth day he ceased voiding, and from then on for thirty-eight hours a total of only 75 cc. of urine was passed. He did not vomit, but the pulse became steadily weaker and he was very restless. Muscular twitchings also developed.

At noon on October 29, the seventh postoperative day, the patient was seen by me in consultation with Dr. Bacon. He then had a history of practical anuria for twenty-four hours, only 50 cc. of urine having been passed since the previous day, though he had taken enormous amounts of fluid. He was very irritable, and twitching of the muscles was evident. The breath was ammoniacal and the eyes sunken. The heart was still slow, but the sounds were weak and the pulse so poor that it could be felt only occasionally at the wrist. The lungs were clear, with no signs of edema. The abdomen was only moderately distended. The liver was not palpable, and dulness was normal. The extremities were cold and blue. The blood pressure was only 50 mm. systolic.

It was decided to give an infusion and to take blood to be tested for nonprotein nitrogen at the same time. The following diagnosis was made: (1) anuria, (2) renal failure, (3) probable vasomotor failure, since the heart was apparently normal, and (4) probable azotemia. Apparently this was a case of vasomotor failure resulting in a blood pressure so low that the kidney was mechanically unable to secrete urine.

An infusion of 100 Gm. of dextrose was given in a 50 per cent solution followed by the administration of 1,500 cc. of saline solution. There was 155 mg. of nonprotein nitrogen per hundred cubic centimeters of blood. The reaction to this treatment was spectacular. The patient went to sleep during the infusion and

became free from irritation and muscular twitchings. He slept for about two hours afterward. The blood pressure rose to 90, and the pulse had good volume and was slow. He still took fluids wells.

At about 3 p. m., he began to be restless again and the muscular twitchings recommenced. The blood pressure dropped to 50 systolic and the pulse was weak, though not nearly so weak as before. He had not secreted urine since the first infusion, so I catheterized him, but only about 20 drops was obtained. Another infusion was given and 100 Gm. of dextrose was given intravenously in a 50 per cent solution, followed by the administration of 1,500 cc. of saline solution. Again the effect was good, and the patient fell asleep during the infusion. The improvement was short-lived, however. Renal diathermy was tried, but proved ineffective also. At this time the nonprotein nitrogen was 170 mg., a rise of 15 mg. (in spite of the large infusion) occurring in three and one-half hours.

The patient became more wild, the muscular twitchings were more marked and the pulse soon relapsed to a very weak beat. The heart sounds were distant, and the blood pressure fell again. He still took fluids well.

At 9 p. m., the patient was seen by Dr. George Blumer who obtained the same physical findings as were noted at noon and in the afternoon. The blood pressure had fallen to 60 mm. The extremities were cold again and the pulse barely perceptible. It was Dr. Blumer's opinion also that this was a case of sudden renal failure due to vasomotor dysfunction and resulting from inability of the kidney to secrete urine at such a low blood pressure.

It was felt that any procedure would prove to be only palliative, and so he was made comfortable with the administration of scopolamine hydrobromide and morphine.

Until about 10 p. m. he took fluids well and did not vomit, but from then on he had severe hiccups and vomited. He died at 2 a. m. on the following morning. The nonprotein nitrogen was 240 mg.

During the last thirty-eight hours of his life he took by mouth more than 4,500 cc. of fluid and received by infusion 3,400 cc. of fluid. The total of 7,900 cc. is large, but during this period he did not secrete more than 70 cc., at the most.

This was a case of anuria with uremia. The blood pressure was low; there was every reason to suppose that the heart, kidneys and liver would be normal, and at autopsy this proved to be the case.

Autopsy.—Autopsy was performed by Dr. Charles J. Bartlett, pathologist, at the Grace Hospital, on October 30. The body was that of a well developed and well nourished man. Rigor mortis and postmortem lividity were present. There was purging from the nose. The abdomen was moderately distended. There was no edema of the ankles. There was an open appendectomy wound about 12 cm. in length with gauze packing.

When the peritoneal cavity was opened, the small intestine was found to be distended with gas, moderately congested and the coils slightly adherent by lymph. There was no general peritonitis or fluid in the peritoneal cavity. Examination of the site of operation showed the field walled off, with no collection of liquid. No drain was present, but there was gauze in the operative wound, extending to the lower part of the abdominal wall. It was such a wound as would be expected in appendectomy in a case of gangrenous appendicitis without generalized peritonitis.

No fluid was found in either side of the thoracic cavity. Both lungs were free. They were rather large and overlapped slightly in the median line. The height

of the diaphragm on the right side was at the fourth rib; on the left side, at the fifth interspace. The heart was of normal size, weighing 310 Gm. The myocardium was firm and of good color. The vessels and coronary arteries were normal. Both lungs showed acute congestion and edema, particularly in the lower lobes, apparently a terminal process. There was some emphysema of the upper lobes.

The spleen was of normal size, weighing 120 Gm. It showed a slight enlargement of the malpighian bodies. The pancreas appeared normal. The stomach and the intestines were normal, except for the distention of the intestines by gas and congestion, and the operative condition at the site of the appendix. The liver weighed 1,740 Gm. It was smooth on the surface and somewhat pale as though there might be some acute parenchymatous degeneration. The suprarenal capsules appeared normal. The combined weight of both kidneys was 280 Gm. The capsules of the kidneys were only slightly more adherent than normal, leaving a granular surface in a few small areas when removed. The cortex was of good thickness and somewhat paler than normal; there was probably a slight cloudy swelling. The bladder was contracted and appeared normal. The prostate was not enlarged. The aorta was smooth and elastic. The following anatomic diagnosis was made: recent operation on appendix; intestines congested and distended; no general peritonitis; acute congestion and edema of lungs; slight cloudy swelling of kidneys and liver; cause of death not apparent from the gross anatomic observations.

On microscopic examination, sections of the kidneys showed that the glomeruli were apparently normal; there was no recognizable increase in connective tissue, and only a small amount of acute parenchymatous degeneration. The liver showed only a slight acute parenchymatous degeneration. Examination of the other organs added nothing to the gross description.

COMMENT

In the light of the normal observations at autopsy, this would appear to be a case of true uremia due to purely mechanical factors: the inability of the kidney to secrete urine at such a low blood pressure, and the consequent rise in the nitrogen factors of the blood. Apparently the basic failure was of vasomotor origin, but what lay behind this is a matter of conjecture, as the suprarenal glands were normal. When compared with cases of scarlet fever and mercury poisoning, the time from the onset of anuria to death was exceedingly short, and this might lead one to suppose that the nitrogen had already mounted to a high point before the anuria began. Possibly this process had begun at the time of operation, but if that were the case, one would expect to find evident changes in the renal tissue.

Though this condition might come under the group termed by Atchley "medical shock," the cases described by him showed signs of circulatory failure, such as edema of the lungs and dyspnea, and did not show a marked rise in the figures for nitrogen. My patient did not have such signs at any time until immediately ante mortem.

Certainly, the amount of fluid taken by the patient through the mouth and introduced by vein was sufficient to give volume to the

circulation. Therefore, it would seem that the failure to maintain a normal blood pressure was due to some factor other than the volume of the blood or the heart. The only remaining factor that can be called to account seems to be the tone of the arterial and venous systems. Had there been a complete relaxation of these muscles with a resulting widening of the vascular bed, a sudden and continued fall in blood pressure might have developed. If this was the case, the only means at hand to combat the condition were used unsuccessfully.

To return to the physiology of the kidney, in this case there was a change in the blood pressure. This change was dependent on the tone of the blood vessels, which was so low that normal blood pressure could not be maintained in spite of what was believed to be adequate treatment. Failure of this type may have been due to toxicity from the gangrenous and ruptured appendix or it may have been a more fundamental inadequacy, since the patient had had a low blood pressure one year previously, when he was refused life insurance because of hypotension. There may even have been a congenital inadequacy in the nerve supply of the vascular structure, which was not severe enough to cause trouble under normal conditions but which could not withstand the sudden strain of an operation. At any rate, in this case apparently an azotemic death occurred, owing to mechanical failure of the kidneys resulting from a blood pressure so low that the kidney could not secrete urine, though the kidneys, the heart, the suprarenals and the liver were undamaged.

EFFECT OF INGESTION OF WATER AND OF DEXTROSE SOLUTION ON EMPTYING TIME OF NORMAL STOMACH *

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Trainers and coaches of athletic teams generally prohibit the ingestion of fluid by players during the hour immediately preceding athletic contests. One of the popular reasons for this prohibition is the belief that fluid taken prior to the game remains in the stomach (the stomach becoming "water-logged") and may cause nausea and vomiting, thereby impairing the player's efficiency. In recent years it has been a common practice to give athletes, such as football players, carbohydrate by mouth to supply readily available energy and to avoid hypoglycemia, which has been shown by Levine and Gordon [1] to occur in marathon runners. The purpose of this study was to determine the emptying time of the stomach in healthy young men after the ingestion of water and of dextrose solution during periods of rest and exercise.

No evidence was found in the literature to support the popular belief that ingested fluid "water-logs" the stomach if taken prior to athletic contests or during exercise. Apparently accurate experiments on exactly this aspect of gastromotility have not been made previously. However, there have been a few investigations of problems closely related to the one under consideration. The earliest observations on the emptying time of the stomach were those of William Beaumont,[2] the great pioneer physiologist, on his patient, Alexis St. Martin, who suffered from a permanent gastric fistula. Dr. Beaumont believed that moderate exercise favors rapid digestion by increasing the circulation of the system and the temperature of the digestive tract. Fatiguing exercises, in his opinion, retard the process of digestion. He presented two reasons for these conclusions: "the debility following hard labor, of which the stomach partakes; and the depressed temperature of the system, consequent upon perspiration and evaporation from the system." He also stated that fluids of all kinds pass out of the stomach soon after they are received.

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* From the Department of Roentgenology, University Hospital, Ann Arbor, Mich.

1. Levine, S. A., and Gordon, B.: Some Changes in the Chemical Constituents of the Blood Following a Marathon Race, with Special Reference to the Development of Hypoglycemia, J. A. M. A. **82**:1778 (May 31) 1924.

2. Beaumont, William: Experiments and Observation on the Gastric Juice and Physiology of Digestion, Lilly, Wait & Wait & Company, Boston, 1834.

Series of experiments were conducted by Nielsen,[3] who selected a group of twenty persons (ten men and ten women) without gastrointestinal symptoms. He examined them by fluoroscope after the ingestion of a meal composed of gruel, 300 Gm. of rice flour and 100 Gm. of barium sulphate. The first series of experiments was made with the subjects resting in bed, the second with the same subjects walking about. He found that the average emptying time of the men's stomachs was thirty-seven minutes longer while resting in bed than while walking, and that of the women's stomachs thirty-four minutes longer while resting than while walking.

Campbell[4] studied the gastric content and emptying time of the stomach by fractional extraction with a Ryle tube and by complete withdrawal of the gastric contents at the end of two and one-half hours. In most of his experiments the subjects were seven healthy young men, and the ingesta consisted of a "porridge test meal." He found that exercise (running slowly for 2 or 3 miles) retarded the secretion of gastric juice and decreased the rate of emptying.

For our experiment fifty healthy college students were selected, none of whom remembered having had symptoms of indigestion. All of them were available for the first, or rest, phase of the experiment, and twenty were available for the second, or exercise, phase. They were instructed to abstain from food and drink of any kind after 7 p. m. and to appear at the roentgen department of the University Health Service at 9 a. m. the following morning. Each was given about 500 cc. of water containing 1 tablespoonful of skiabaryt, which is 75 to 85 per cent barium sulphate U. S. P., admixed with sugar, tragacanth cinnamon, vanillin and cacao. This mixture contains just enough opaque material to outline the stomach satisfactorily. Each subject was observed with the upright fluoroscope at fifteen minute intervals until the stomach was empty, and then a flat film of the abdomen was taken. Between observations they were allowed to sit down or stroll around the building as they pleased. The second, or exercise, phase of the problem was carried out with exactly the same technic except that between periods of observation the subjects ran continuously. They ran around the campus or the gymnasium track until it was time to appear for another observation. This procedure was continued until fluoroscopic examination showed the stomach to be empty.

The accompanying table records the results of the observations with both water and dextrose during the periods of rest and exercise. After the ingestion of water, while the subjects were at rest the average

3. Nielsen, A.: Roentgenological Examination of the Motility of the Stomach in Healthy Individuals During Rest and Motion, Acta radiol. **1**:379, 1921-1922.

4. Campbell, J. M. H.; Mitchell, G. O., and Powell, A. T. W.: The Influence of Exercise on Digestion, Guy's Hosp. Rep. **78**:279, 1928.

emptying time of the stomach was sixty and three-tenths minutes. In thirty-seven of the men, or 74 per cent of the group of fifty subjects, the stomach emptied during the first hour. Of the group of twenty who ingested water and then exercised, fifteen, or 75 per cent, showed total gastric evacuation in forty-five minutes. The average emptying time for the group of twenty was thirty-nine minutes. After the ingestion of a 50 per cent dextrose solution, the average emptying time of twenty subjects at rest was sixty-four and one-half minutes. Fourteen, or 70 per cent of the subjects, showed complete gastric emptying during the first hour. The average emptying time of the same group on taking dextrose solution and exercising was forty-two minutes. Fifteen, or 75 per cent, showed complete gastric emptying after the first forty-five minutes.

It is evident that the difference in the emptying time of the stomach after the ingestion of water and of dextrose solution is neglible. On the other hand, relatively strenuous exercise appears to shorten definitely

Emptying Time of the Stomach in Four Experiments

	500 Cc. Water + 1 Tablespoon of Skiabaryt				500 Cc. 50% Dextrose Solution + 1 Tablespoon of Skiabaryt			
	Rest		Exercise		Rest		Exercise	
Emptying Time	No. of Cases	Per Cent	No. of Cases	Per Cent	No. of Cases	Per Cent	No. of Cases	Per Cent
In 30 minutes.....	5	10	9	45	1	5	8	40
In 45 minutes.....	14	28	6	30	6	30	7	35
In 60 minutes.....	18	36	5	25	7	35	4	20
In 75 minutes.....	7	14	0	0	2	10	1	5
In 90 minutes.....	3	6	0	0	2	10	0	0
In 120 minutes.....	3	6	0	0	2	10	0	0
Total cases studied.....	50	100	20	100	20	100	20	100
Average empyting time	60.3 minutes		39 minutes		64.5 minutes		42 minutes	

the emptying time after the ingestion of either water or dextrose solution. It is possible that the difference in results between the groups without exercise and those with exercise might have been greater had the former been completely at rest in a reclining position during the period of observation. In these observations no relation between the emptying time of the stomach and the type of habitus of the subject could be determined. The so-called gastroptotic or long stomach was as common in young men with good abdominal muscles as in those who were thin and had less developed muscles. It is noteworthy that rest and exercise seem to have little effect on the individual variations in the emptying time found in this group. Stomachs that required a longer time than the average to empty during rest also regularly required longer than the average time to empty during exercise. Similarly, rapid gastric evacuation was seen in the same person during both rest and exercise.

The experiments of Campbell are of particular interest. Running, even at a moderate pace, would ordinarily be considered fairly vigorous exertion. This form of exercise, which apparently retarded the emptying of the stomach in his subjects, seemed to accelerate it in our subjects. This apparent discrepancy may be due, in part at least, to the difference in ingesta. Oatmeal porridge requires a certain amount of gastric digestion, while water and dextrose solution are simply fluids to be expelled, a process that, as Beaumont suggested, occurs relatively quickly. Furthermore, Campbell pointed out in his experiment that the retardation in the time of digestion and emptying of the stomach seemed proportional to the amount of distress caused by the exercise. The young men used in our experiment were vigorous and of athletic habits, and the running in which they indulged during the observations did not distress them.

CONCLUSION

1. The emptying time of the stomach was determined fluoroscopically in fifty healthy young college students after the ingestion of 500 cc. of water and of an equal quantity of 50 per cent dextrose solution containing a very small quantity of barium sulphate, with the subjects sitting or walking about, and in twenty cases with the subjects running continuously between observations. The total number of experiments on the fifty students was one hundred and ten.

2. No difference was observed in the rate of emptying of dextrose solution and of water in either group.

3. Exercise (running) seemed to produce a definite acceleration in the emptying time of the stomach. In these experiments, as exercise accelerated the emptying of the stomach, it seems justifiable to conclude that dextrose solution in a palatable form could be administered to athletes before a contest in which readily available fuel is required, without fear of producing gastric retention.

Dr. F. Lynam, the physician of the Athletic Association of the University of Michigan, and Miss Mary Zeile assisted me in carrying out these studies.

Book Reviews

DIFFERENTIAL DIAGNOSIS IN PEDIATRICS. By DR. W. PFLUGER, with a foreword by PROF. DR. J. HUSLER. Price, 73 marks. Pp. 160. Dresden: Theodore Steinkopff, 1931.

This modest little text differs materially from some of its predecessors in the same field in that emphasis is placed primarily on the symptomatology of disease. The interpretation of symptoms leads to a practical discussion of every phase of differential diagnosis.

The important and essential procedures at the bedside are stressed, and are presented in simple, lucid fashion.

The subject matter treated is amazingly extensive and comprehensive for so small a book. In connection with one or several outstanding symptoms, such as cyanosis or pallor, hyperpyrexia, convulsive seizures, hemorrhage of various forms, icterus, vomiting or diarrhea and many others, every conceivable disorder in any way related to the symptom and common to the given age level of the infant or child is discussed and clearly analyzed from the standpoint of differential diagnosis.

In such discussion, again, the primary and most likely disorders, or disorders related in any way to the symptom or symptoms, are exhaustively dealt with, along with at least mention of all other possibilities.

The size and nature of the text precluded any theoretical or academic discussion of disease, etiologically or otherwise, and it is wisely omitted, as it would certainly rob the book of its simplicity and lucidity and would probably tend to confuse rather than to guide the reader.

To the perplexed practitioner this type of book is a vade-mecum and a practical guide which for quick orientation and substantial useful help will prove far superior to many a ponderous text or handbook.

The author's style is excellent, and the diction is exceedingly clear and direct. One senses immediately that the book is written by a practitioner who has sensed in lively fashion the needs and shortcomings of his average fellow practitioner in pediatric practice.

DIE REFLEKTORISCHE SELBSTSTEUERUNG DES KREISLAUFES. By PROF. DR. MED. EBERHARD KOCH, Nauheim. Paper. Price, 18 marks. Pp. 234, with 44 illustrations. Dresden: Theodor Steinkopff, 1931.

This monograph contains a well organized and critical summary of the present available information on the influence of the sensory nerves distributed to the heart, the aorta, the carotid sinus and other blood vessels, and on the reflex regulation of the heart itself and of the blood vessel musculature in health and in disease. That sensory nerves distributed to the walls of the ventricles and to the aorta contribute to cardiovascular reflex control has long been known. A number of years ago the work of a German physician, Hering, brought out the fact that there is an additional pronounced sensory region at the bifurcation of the carotids (the so-called carotid sinus) from which sensory impulses play a marked rôle in the cardiovascular reflexes. Later, though still fragmentary, information indicates that probably all blood vessels are supplied with afferents having important cardiovascular reflex function. The disturbance of these mechanisms in such pathologic conditions of the blood vessels as sclerosis or aneurysm is as yet imperfectly understood but constitutes an important problem of investigation in internal medicine.

The author handles the data, the problems and the theories in a clear and critical manner. The monograph is a distinct contribution to medicine and may be perused with profit by all students of medicine and physiology.

GONORRHEA IN THE MALE AND FEMALE. A BOOK FOR PRACTITIONERS. By PERCY S. PELOUZE, M.D., Associate in Urology and Assistant Genito-Urinary Surgeon at the University of Pennsylvania; Fellow of the Philadelphia College of Physicians. Second edition, revised. Cloth. Price, $5.50 net. Pp. 440, with 92 illustrations. Philadelphia: W. B. Saunders Company, 1931.

This volume will interest every physician who comes in contact with the most prevalent of all diseases. In this second edition of his popular work, Pelouze has added much to the scope of the discussion of gonorrhea, its complications and sequelae, but has not striven for encyclopedic comprehensiveness, nor sacrificed any of the direct simplicity that gives emphasis to his literary style. On the basis of his own wide clinical experience, the author deplores the modern tendency to overtreat patients with gonorrhea. He outlines with considerable clarity conservative and sane methods of management of the disease in its various stages, which have met with gratifying results in his own office and in clinical practice. He does not offer empiric routines to be blindly followed, but makes a commendable effort to rationalize the methods of preference on the basis of the pathophysiologic principles that are involved.

An important addition to the present edition is a section of fifty pages on gonorrhea in the female. The text itself is sincere, vigorous and highly readable. Occasionally the author relieves the seriousness of the problem with quiet and effective humor, such as: "Wherefore, it should be realized that the physician is but a child in the hands of a woman intent upon deception, and he should be willing to bow to the art with admiration for its finer points without greatly disturbing his scientific reasoning and skepticism about immaculate infection."

In the preface to the first edition, the author said, "publicly unspeakable and medically outcast, gonorrhea has limped through the ages a veritable 'nobody's child.' It is a serious disease, and it needs serious attention." This splendid book gives the disease just that.

NUTRITION AND DIET IN HEALTH AND DISEASE. By JAMES S. MCLESTER. Second edition. Price, $8.50. Pp. 891. Philadelphia: W. B. Saunders Company, 1931.

This comprehensive study by McLester includes nutritional requirements for normal adults and children as well as diet in disease.

The chapter on the normal diet emphasizes the fundamental considerations by which one must be governed for the proper selection of food. Man's dietary needs are outlined in a base ration as suggested by E. V. McCollum.

Infant feeding is discussed in a special chapter by Dr. McKim Marriott of Washington University, St. Louis. The feeding of surgical patients is outlined by Dr. Barney Brooke of Vanderbilt University, Nashville, Tenn.

For the chapters on nutrition in disease, the literature of recent years has been gleaned for therapeutic and experimental diets. These are reprinted in full or in part, with comments.

This compilation of diets in disease is a great time-saver for the nutrition worker, and the extensive bibliographies are valuable.

Menus and recipes are reprinted, which are helpful to use as patterns in planning diets to meet the requirement of the individual.

The tables and charts of a general nature that are reprinted are adequate for calculation of diet.

ENTSTEHUNG, ERKENNUNG UND BEHANDLUNG INNERER KRANKHEITEN. By DR. LUDOLF KREHL, Professor in Heidelberg. Band II.: Die Erkennung innerer Krankheiten. Paper. Price, 12.80 marks. Pp. 172. Berlin: F. C. W. Vogel, 1931.

This volume on diagnosis in internal medicine represents the second in Krehl's trilogy on the pathogenesis, diagnosis and treatment of internal diseases. The term "diagnosis" is used in the broadest sense and therefore includes "Beurteilung,"

or the physician's considered judgment about the entire medical situation. What the latter amounts to in socialized Germany is brought out vividly, but dispassionately, in the first chapter. Those who are interested in so-called state medicine as it exists in Germany should read this chapter more than once. Krehl's entire philosophy of the place of medicine among the sciences and arts, his concepts of the physician's relation to the patient, his general advice as to the technic of the anamnesis and the synthesis of the data obtained, and a host of other details derived from the mature experience of this very human master of the Heidelberg Clinic make this chapter a work of art.

The remainder of the book is devoted to a systematic consideration of the general examination of the patient, infectious diseases and disturbances of the various systems. It is difficult to describe the material of these chapters because it is a mixture of high lights in physical diagnosis, laboratory methods, shrewd clinical intuition and delightful personal comments. It takes an unusually mature medical student to digest such stuff, but it is worth a little effort. The discussion of clinical disturbances of the circulation, respiration and formation of urine is particularly excellent. There are a few, but pertinent, references to the literature and frequent cross-references to the volume on pathologic physiology.

L'AEROPHAGIE. By A. DOBROVICI. Price, 10 francs. Pp. 31. Paris: Gaston Doin, 1930.

The author presents an excellent and logical treatise on aerophagia. He defines the condition as the swallowing of atmospheric air which may or may not be followed by belching. Physiologic aerophagia is discussed. Pathologic aerophagia is said to differ from the physiologic form either by the greater size of the air bubble in the stomach, or by the intolerance of air in a hypersensitive stomach and the dyspepsia and mechanical troubles that accompany distention of the digestive tube with air. The mechanisms of the unconscious swallowing of air are described.

Air is said to penetrate for varying distances in the digestive tube with the production of corresponding symptoms: 1. Eructation may be provoked simply by the accumulation of air partly swallowed into the pharynx. 2. Air penetrates more or less into the esophagus but does not reach the stomach and is rejected immediately through the mouth. 3. Air penetrates into the stomach, partly opening the cardia, and comes out afterward as eructations. 4. Air gets into the stomach in great quantities, is stored up there, causing distention, and is finally ejected by violent belching. 5. The swallowed air, after distending the stomach, passes through the pylorus and distends the intestines, and the act is completed when the air is expelled as flatus.

Treatment consists largely of explaining the mechanism of aerophagia to the patient. The necessity for his cooperation is emphasized.

BLUTKRANKHEITEN UND BLUTDIAGNOSTIK: LEHRBUCH DER KLINISCHEN HÄMATOLOGIE. By OTTO NAEGELI. Fifth revised edition. Price, 86 marks. Pp. 704, with 104 illustrations. Berlin: Julius Springer, 1931.

Naegeli's clinical hematology in its fifth revised German edition probably contains as comprehensive analyses and descriptions of the various technics of examination of the blood as any text now published. It includes much more detailed information concerning the various morphologic structures and physicochemical constituents of the blood than any of the usual texts on laboratory technic. These matters concerning the various technical procedures, stains, morphology and variations of the erythrocytes and leukocytes are treated with attention to minute detail and a comprehensive bibliography. Many colored illustrations add greatly to the text. Extensive discussions are made, respectively, of the anemias, pernicious anemia, leukemia, pseudoleukemia and the changes of the blood with infectious diseases, helminthiasis, malignant tumors, poisons and blood toxins. Shorter sec-

tions are devoted to changes of the blood with paroxysmal hemoglobinuria and with diseases of the glands of internal secretion. Advanced students in hematology and clinicians, especially in internal medicine, will find this text valuable.

CHININ IN DER ALLGEMEINPRAXIS. By DR. MED. FRITZ JOHANNESSOHN. Paper. Pp. 232, with 3 illustrations. Amsterdam: Bureau Tot Bevordering van Het Kinine-Gebruik, 1930.

After a brief historical introduction, the author discusses briefly the pharmacognosy and chemistry of quinine as well as the fate of the drug after absorption. By far the greater part of the book is given over to a consideration of therapeutic uses of quinine in diseases other than malaria, which is discussed in less than a dozen pages. From the evidence presented, one may gain the impression that quinine is indicated in a great variety of infectious diseases (pulmonary diseases, pertussis, erysipelas, etc.). However, surprisingly few authors who do not attribute their success to quinine or who have obtained untoward results are cited in the detailed discussion of many diseases which one rarely associates with quinine therapeutically. The author also cites numerous references to the use of the drug in disturbances of cardiac conduction, in the initiation of labor and in the treatment for varicose veins and hemorrhoids.

Quinidine is discussed in a separate chapter.

The book is indexed. The bibliographies contain 809 references.

LAGOUTTE. By DANIEL CRITZMAN. Paper. Price, 25 francs. Pp. 235. Paris: Gaston Doin, 1931.

This recent monograph on gout, given in French by a Roumanian who spent his professional life in France, has been revised posthumously by Jacques Forestier. It comes at a time when gout is receiving relatively little attention in the clinical literature of this country, owing, apparently, to the widespread belief that this is a rare disease.

The book contains the usual excellent clinical descriptions of the various stages and types of gout for which the French school is particularly noted. The principal theories of pathogenesis with the augments pro and con are briefly discussed. In dealing with treatment, the author decries the modern tendency to proscribe all purine-containing foods, and he believes strongly in the more didactic methods of choosing the diet on the basis of experience. Medically, there is nothing new or successful. Those who have to deal with gout may well find much of value to them in this volume.

TABLES OF FOOD VALUES. By ALICE V. BRADLEY, B.S., Supervisor and Instructor of Nutrition and Health Education, State Teachers College, Santa Barbara, Calif. Price, $2. Peoria, Ill.: The Manual Arts Press, 1931.

This book of food tables should prove very useful to any one engaged in work on nutrition. It is written in a practical and concise form and includes recipes that enable the reader to know the formulas used in the computation of the foods listed.

The food tables are presented in the following manner: kind of food, measurement, weight, grams of protein, fat and carbohydrate, calories, mineral shares, vitamins, value as a source of bulk and acid and basic reactions.

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